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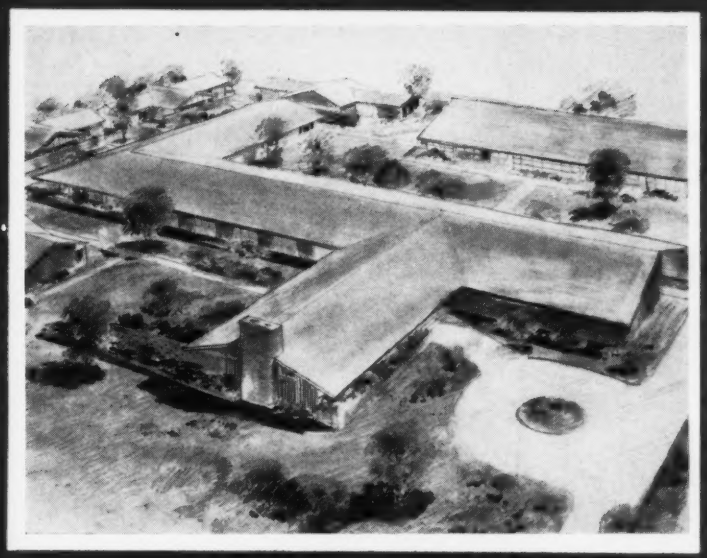

COMMUNITY APPROACH TO THE SENIOR CITIZENS PROBLEM, PAGE 261

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Editorials

A Statement at the Committee Hearing in the House of Representatives on S.B. 20

Mr. Chairman and members of the Committee, I represent the Department of Pediatrics, University of Oklahoma School of Medicine, and its advisory committee. As we studied this bill and its relation to us in the department it seemed to us that somebody, who is not afraid of losing his job, ought to represent the children. If I may I would like now to say a word for the children.

It seems to us a strange bit of biologic reasoning on the part of the law makers that a child who is growing and exercising and developing for which he needs the expensive protein foods, milk, eggs, and meat, is allowed less in his grant for food than is an old person who probably should be cautious of excessive protein intake since he is neither growing, developing nor apparently doing much in the way of exercise. Many, many times I have talked to a mother in the Out-patient Department at Children's Hospital about the nutritional status of her poorly-nourished child and been told that all she had to live on was grant money and she could afford milk and meat only occasionally. These children cannot possibly develop their full potential of physical and mental and emotional health on the money allowed them in their grant. The stipulated amount of $24 for food means nothing when only $6 is allowed for everything else. We, in pediatrics, know no better way to make an incompetent, inadequate adult than to starve him during his period of growth. What sort of progeny can people like that possibly have? There could be no better scheme devised for perpetuating the assistance rolls.

The strange part of it is that the economic upgrading of the old age pensioner has been what we would consider a relative if not actual down grading of the ADC child. In 1937 OAA received 75% of the assistance funds and today gets 76%. Whereas the ADC program received 17% of the total fund in 1937 and today only 13%. Today a mother and one child receives a maximum of $110 a month and an old age pensioner and his wife a maximum of $148.

A mother and four children have in their grant a total of $14 for clothing, a total of $9 for household remedies and a total of $5 for personal items. Five old-age pensioners get $30 for clothing, $35 for household remedies and $45 for personal items. That is roughly two times, four times, and five times as much respectively. Of the Assistance Fund, 76% goes to 100,000 people in the old-age group and 13% to ADC for 44,000 children and 14,000 caretakers. In other words, less than twice as many people get almost six times as much of the Assistance fund. It isn't that the old people get so much: its that the children get so little.

It is small wonder that these children should look like urchins—and nothing would be more apt to make them behave like urchins than to look like urchins. There is a word used in scientific language to describe the phenomenon of the old eating up the young. The word is infantophagia and it would appear to be almost applicable here, and this at a time when our society is dedicated to the promotion of physical and mental health in its young and to the prevention of juvenile delinquency. And still there are those who have the temerity to come out here and ask you to refuse assistance with sales tax money to medically indigent children for hospital care when it was the clear intent of the people in adopting Article 25 and of the legislature in its first allocation of funds to include this category of assistance in the assistance fund; and this without a shread of evidence that grants for the old age assistance would have to be cut. This is an assistance fund and primary resources have to apply first—so that as more and more people coming on the old age rolls have some social security there is less state money needed to fill the amount of the grant, unless these people should decide they ought to take proper care of their young—and I have a feeling that for the most part, it is actually their young.

Out of a very fine thing that the legislature did in establishing the Assistance Fund for our less fortunate citizens there has been built a Frankenstein which we believe you gentlemen have the courage to contain. You could well begin by assuring an adequate medical care program for medical indigent children by passing this bill which takes that money first before anybody has a chance to get at it to increase the grant in any category.

The problem is a very simple one of solution but in order to solve it the members of the Legislature need to feel the backing of all of us. It is quite obvious that the category of assistance to ADC children and to medically indigent children is not adequate. The Crippled Children's Commission lacks, under its present funds, about $500,000 of having enough money to pay hospitals for the service they rendered to children who are eligible for inclusion under the Crippled Children's program.

The assistance program for old age re-

cipients is truly an assistance one which means that primary resources must be applied first. The majority of people now coming on the rolls of OAS have some social security. The state can subtract this amount from the recipient's monthly grant. During the period of transition from a pension group, who had little or no social security to one in which most of them do, a surplus of about $1,000,000 a year will accrue. Should the people of the state have their saving on this applied to insure more adequate assistance where it is needed and take care of other assistance problems that are now being taken care of out of the general revenue fund which can be legitimately added to the assistance program or should the saving be used to further discriminate against the unfortunate in other categories of assistance in favor of the old age pensioner?—*B.H.N.*

Blood Dyscrasias and Drugs

"There are some remedies worse than the disease"—Publius Syrus, Maxim 301

A problem seen by all physicians is the patient who, during the course of therapy, develops pancytopenia or depression of one of the cellular elements of the blood. Often such a patient is receiving several drugs and frequently the disease is one known to produce such adverse reactions. At times the problem is simple—the patient does not require the therapy, and stopping all medicaments results in a return to normal. One internist attributes his stature as a consultant to his willingness to stop all drugs. Knowledge of which agents can produce these toxic effects is important for the proper management of such patients.

Help with these problems is now available in the information supplied by the Subcommittee on Blood Dyscrasias of the Committee on Research, Council on Drugs, of the American Medical Association.[1] They have collected information which is published in a summary form and distributed to State and County Medical Societies, approved hospitals and medical schools. This summary lists agents whose administration has been associated with depression of the hemopoietic system.

The committee properly cautions that judgment must be used in interpreting the material since the fact that a drug appears does not necessarily indicate that it is harmful or that it is the cause of the dyscrasia reported. The summary divides the reports into three groups: (a) reports in which only one drug or chemical substance was listed as the possible etiologic agent, (b) reports in which more than one substance was given—one or more of which is known to cause blood dyscrasias frequently, and (c) reports in which multiple substances were listed as the possible agents none of which is known to cause blood dyscrasias frequently.

A total of 427 cases are included in the most recent summary. Fifty-eight agents are included in the (a) group, i.e., reports in which only one drug or chemical substance was listed as the possible etiologic agent. This group warrants additional consideration. The Big Eight in this group, i.e. the agents listed more frequently and in the order of frequence were chlorpromazine (Thorazine), chloramphenicol (Chloromycetin), promazine HCl (Sparine), 5, 5-diethyl-2-thiobarbituric acid, phenylbutazone (Butazolidin), quinidine, sulfisoxazole (Gantrisin), and propylthiouracil. Pancytopenia was reported with 32 agents; leading this group were chloramphenicol and phenylbutazone. Leukopenia was reported with 27 agents; heading the list for this group were chlorpromazine and promazine HCl. Thrombocytopenia occurred associated with 12 agents; the leaders were quinidine and acetazolamide (Diamox). Anemia occurred with only four agents and only one, salicylazosulpyridine (Salazopyrin), was reported more than once.

This list does not provide information concerning the amount of the various agents prescribed, so that one drug on the list may actually have a lower reaction rate than some other drug if the first agent is used with greater frequency.

Among the interesting agents listed were slippery elm and syrup of wild lettuce. These last appeared in the U. S. Pharmacopeia in

1920[2] and 1910[3] respectively. Neither appear in three current text books on therapeutics.[4,5,6]

Slippery elm was used extensively in medical practice as a demulcent and in baseball as an aid in lubricating the ball to deliver a spitball, a practice outlawed since 1920.[7] Syrup of wild lettuce had considerable vogue as a soporific and cough medicine until it was discovered that the most popular preparation also contained morphine. It is presumed that these drugs were administered by a well-meaning member of the family in some remote hill country.

To return, however, to the main point. Physicians are asked to supply information about patients who demonstrated depression of the hemopoietic system while receiving a drug or drugs.[7] The reports will be summarized by the committee and distributed. The summaries should be filed in the hospital library so that they are readily available since their proper use may be of considerable importance to some patients, or at least may console some perplexed physician who may thereby discover that another physician was also confronted with a similar dilemma.

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8. Proper forms may be obtained by writing to the Secretary, Committee on Research, American Medical Association, 535 N. Dearborn, Chicago 10, Illinois.

—*J.F.H.*

Service Contracts for Elder Citizens

The annual Blue Shield Professional Relations Conference was held in Chicago at the Drake Hotel on February 9, 10 and 11th. The program represented the most outstanding group of participants ever assembled to address this important meeting. This year the presidents of all State Medical Associations were also invited as a means of informing them of current progress among Blue Shield Plans to implement the recent A.M.A. action calling for the development of special forms of medical care coverage for our senior citizens.

Speakers at this conference included Doctor Louis M. Orr, President-Elect, American Medical Association; Doctor Donald Stubbs, Chairman, Board of Directors, Blue Shield Medical Care Plans; Doctor Leland S. McKittrick, Chairman, Council on Medical Education and Hospitals, American Medical Association; Doctor Carlton E. Wertz, President, Blue Shield Medical Care Plan; and many others. The registration at this meeting numbered 298, of which 180 were doctors.

As President of the Oklahoma State Medical Association, I attended the meeting and was privileged to participate in a study group with Doctors McKittrick, Stubbs, and some fifteen other doctors, where they discussed the problem of providing support for voluntary medical care plans for the aged, in an effort to protect this group from having to surrender another of its precious freedoms to bureaucratic control. As indicated in my "letter" of the last issue, it seems evident that Oklahoma physicians should take a realistic attitude toward this problem and work toward the suitable design of a service type contract for this segment of our population.—*E.C.M.*

*Address of The Honorable Orville L. Freeman, Governor Of The State of Minnesota**

I am indeed happy to have this opportunity to welcome you to Minnesota, and to express on behalf of the people of our state our pride and our pleasure in your holding these meetings here.

At the outset, here in Minnesota I am personally deeply grateful for the help and cooperation that I have received from many leading members of your profession. They have given their time and talents to help in solving many problems. They have given me valuable assistance and advice. And as I welcome those of you who are here from outside our state, may I express heartfelt thanks to those of you who, as citizens of Minnesota, have done so much to advance our program.

We are deeply conscious of the debt of gratitude we owe to the medical profession. As individuals, we depend on you to safeguard and restore the personal health that we find so essential to full enjoyment of all the other satisfactions we seek. And as members of society we are finding that the problems you are professionally trained to solve are more and more entwined with the social problems and ills of today.

I am, therefore, today going to ask your help and cooperation in finding a solution to one of those problems—one for which I, along with many other public officials, feel a grave responsibility. But before launching my discussion of that particular problem I should like to express: first, some ideas regarding the similarity in interest between the field of medicine and the field of government; and, second, my position with regard to the interrelationships that do and should exist between government and medicine in America today.

Government and the medical profession have similar though not identical interests, for they both exist because of concern for people. The medical profession is concerned primarily with individuals and their health. Government is concerned with how individuals get along in their various relationships with each other. And the trend is that both of these interests are coming closer together.

It seems to be a characteristic of the increasing interdependence of modern life that social and individual problems and ills become increasingly interrelated. A leading physician in Minnesota—for example—was impelled to organize a community effort to provide employment and other services for the aging members of that community because so many of his patients were sick—actually, physically ill—because of worry about retirement and its attendant problems. And in another community in New York where various social services provided constructive occupation for aging citizens, it was found that this group suffered only half the physical ailments normally expected for those of that age.

Countless examples could be cited showing the influence that governmental decisions have on the health problems of individuals of all ages. School programs affect the health of children. Government is called upon not only to guarantee supply of pure water, but in many instances to take steps to prevent the pollution of air. I believe that no one questions the fact that social and political conditions affect individual health, although no doubt there is room for argument as to how great and extensive that effect is.

At the same time, government is increasingly called upon to pay for direct care for individuals. Government now pays the bill for medical care for the medically indigent, an expense that doctors used to carry almost entirely in earlier years—and one that many of them still carry to a very important extent.

One final point should be made in this very brief picture of the interrelationship of medical and governmental problems. The phenomenal progress that medical science has made in recent years has profoundly affected basic problems of government. In no field are the implications more far-reaching than they are in the increased rate of population growth. Must remember that changing and

*Delivered at the A.M.A. 12th Clinical Meeting, Dec. 2, 1958, Leamington Hotel, Minneapolis, Minnesota.

what we like to call advancing in our society brings new challenges and problems as well as new gratifications.

The population of the United States is now growing at the rate of 2½ million a year. By 1965, we may be gaining 5 million people per year. Yet today, in the midst of a post-war boom in the birth rate, our rate of 25 births per 1000 people a year is only half what it was in 1800. The population increase is largely the result of the lower death rate that medical science and other modern developments have brought about.

A little later, I will discuss further the significance of this population growth to problems of government. Now I just want to point out that these problems face us today in part because of medicine's great achievements in prolonging human life.

Turning now to the second point—the relationship between government and medicine—it may be appropriate to meet immediately the question I am sure is in your minds—what about socialized medicine? I know that this question has frequently been the subject of your deliberations. It was a question I was asked in my last campaign.

The term "socialized medicine" apparently means different things to different people. A simple answer as to its meaning might be the providing of medical care through some branch of government. Yet that definition is inadequate for our purpose, because we all take it for granted that government should provide medical care in certain cases —as, for example, in tuberculosis and mental hospitals. We in the United States have asked for and have thoroughly accepted this principle for so long that I feel sure that the most ardent opponents of socialized medicine, by whatever definition, would not ask that government cease that function. Perhaps the term really refers only to the government assuming further functions over and above those which it now has. Or does it more specifically refer to action in which the elements of universality and compulsion are present?

This confusion about the meaning of the term "socialized medicine" is most unfortunate. The term in itself often arouses violent and sometimes emotional disagreement —among some who do not agree on what they are disagreeing about. Semantics, the science of words, then becomes almost as important as substance. We can lose sight of real problems and real issues in our confusion about the meaning of words. I often wonder whether a misunderstanding about the meanings of terms does not often create as much conflict and disagreements as is created by an actual difference in opinion and judgment.

It would be tragic to permit such misunderstandings to delay our progress toward meeting real human need. And therefore, despite the difficulties of semantics and the possible danger of being misunderstood, I want to face the issue as I see it in clear and simple terms.

My purpose today is to review with you a serious problem, not to discuss semantics. Let us consider, then, what functions government does perform, and why.

In any discussion of this kind it is important to bear in mind that in the United States we have traditionally decided such questions on a pragmatic basis rather than on the basis of an ideology or an "ism". We ask, "is it needed?", and "how can it be done best?" Let me illustrate briefly from history.

When Americans, more than a century ago, decided that education should be universal, free, and compulsory they made this decision without considering any "ism" or asking whether they should adopt socialized education. Government provided schools simply because that was the only possible way they could be made available to all.

When government provided hospital and medical care for the victims of long, expensive, chronic ailments such as tuberculosis and mental illness, it did so for similar reasons. It was socially desirable that the people suffering from such ailments be given care and treatment. Very few could afford such long and expensive care. The people asked government to provide it, because that was the only way it could be made

available.

The same principles hold true, I believe, in all other areas where government performs functions relating to medicine. Government provides a substantial share of the cost of educating doctors because it is socially desirable and necessary. Government carries out those public health functions that could be performed adequately in no other way.

In other words, government is not some outside power constantly seeking to aggrandize itself by taking over more and more functions. (I can assure you that no governor, in the midst of a budget-making process, would want to suggest further functions that would create a bigger budget just for the sake of expanding government itself.) On the contrary, government is a democracy, by the very definition of the term, is the institution through which the people seek to make sure certain needs are met that are not adequately met by other means.

Many western European democracies have adopted universal health care programs with some degree of compulsory participation. Such programs are, I believe, what most of you think of when you use the term "socialized medicine." But we in the United States have greater resources and higher standards of income than any of these nations. And we have gone a long way in the development of voluntary programs using the insurance principle to make it easier for people to pay for their medical care. If these programs meet the needs of the American people adequately, there will be no reason for government to be asked to step in.

Personally, I do not want government to be any bigger than necessary. I do not believe in compulsion except where it is essential to achieve a socially desirable goal. But where an essential goal can be achieved in no other way, under our American democratic system, government has in the past, and will in the future be called upon to take care of urgent, unmet needs.

Our goal in the field of medical care for the American people is one on which I am sure the medical profession and government are in total agreement. We want to insure the availability to all Americans of medical care of the best quality, and in sufficient quantity to meet their needs. We must cooperate to achieve this goal. We must work it out together.

I want now to present to you one area in which the problems we face in working toward that goal urgently demand a solution. I want to ask your help in developing a program to meet, more adequately and efficiently, the medical care needs of our senior citizens.

Earlier in this discussion I referred to the population explosion that is taking place. Mere growth in numbers, however, does not give the whole picture. The age distribution of this increasing population is of even greater significance to those trying to meet the changing needs of our society.

For the first time in the history of the United States the dependency ratio in our population is increasing. Up until 1940, those age groups in our population that are usually dependent on others, the young and the old, were steadily decreasing in proportion to those in the productive age group. Since that time, the trend has been reversed.

To show specifically what this means—we have tried to analyze the probable population changes expected in Minnesota from 1950 to 1965. As a whole, our population is expected to increase 22% during that 15-year period. But the increase will not be uniform in all age groups. Those under 21 will increase by 38%, and those over 65 by 35%, while the increase in the productive years between 21 and 65 will be only 9%. Thus, proportionately fewer people in the productive—and taxpaying—years will have to provide for greater educational services for increasing numbers of children and youth, and greater social and medical services for increasing numbers of the aging population.

I am told that progress in medical science may soon change this proportion in the direction of even greater numbers of those over sixty-five. During the past half cen-

tury, our life expectancy at birth has increased 23 years, but our life expectancy at age 65 has increased only 2½ years. These figures reflect the great decline in infant mortality and the success in combatting communicable diseases. Now that constantly increasing attention is being given to research on the diseases of adult years, we can expect that more of us will live longer in the years ahead.

Thus, we face the problem of providing medical care for increasing numbers of older people. Government now is expected to provide such care for those who are on Old Age Assistance. In Minnesota we provide all Old Age Assistance recipients with medical care according to their needs, and we are one of the few states that places no ceiling on expenditures for such care. These medical care costs are constantly increasing. And while social security pensions are reducing the numbers of people who need old age assistance for ordinary living expenses, they are not sufficient to cover expenses of serious and chronic illness. Thus, there are increasing numbers of retired men and women who have earned pensions sufficient to meet their needs as long as they stay well, but insufficient to meet their medical care needs. If and when they become ill, those costs become an increased burden on government.

Inflation has aggravated this problem. It is generally recognized that inflation takes its greatest toll from those living on fixed, retirement pensions. It is not so generally recognized that for older persons the rising costs of medical care are proportionately much harder to meet than other rising costs. Surveys show that, while people past the retirement age need and do spend less on such cost-of-living items as food, clothing and shelter—in contrast they need to spend more on medical care. Their need for such care is probably double that of the average for the pre-retirement years. And, during the past few years the costs of medical care have risen substantially faster than other cost-of-living items.

The seriousness of this situation is dramatized by individual illustrations we all know. For example, one Minnesota farmer of 71 years spent the entire annual gross income from his principal crop—the sale of his sheep—and still had to carry over into the next year a part of the $2,300 medical and hospital bill that he incurred that year. Such misfortunes can very easily bring about the need for outside help for those who are otherwise economically self-sufficient.

State government must, of course, assume the responsibility for those who need assistance. With Old Age Assistance medical and nursing care payments in Minnesota at the annual rate of eighteen and a half million dollars, and increasing at a rate approaching two million dollars a year, we urgently need a better way to meet this problem. Thus far private, voluntary insurance programs—however rapidly they have grown as a whole—are least effective for the age group over sixty-five. Employee group programs often cease with retirement, and premium costs for individuals of that age are generally too high for them to pay.

It is because of this great need that legislation has been proposed in Washington—and, no doubt, will be proposed again—to expand the federal social security program to include hospital and medical insurance benefits under Old Age and Survivors' Insurance. It was introduced at the last session of Congress in the Forand Bill, which, I believe, you officially and vigorously opposed.

Now, you certainly have the *right* to oppose such legislation if you believe it would be harmful to your profession. You have the *duty* to oppose it if you believe it would be harmful to the public. But if you do oppose it you also have the responsibility of helping to work out an alternative program to meet the need that we all know exists and becomes more serious every day.

A solution is urgently needed. Our costs for medical care for the aging must compete with increasing demands for greater expenditures for education and for mental health, and for scores of other urgent demands. The burden on state government for increasing services is constantly getting heavier in every field. States are assuming a greater proportion of responsibility in non-defense spending—where in 1940 the states

provided 58% and the federal government the other 42%, the states in 1956 were providing 73%. If state governments are going to meet this increased share of constantly growing responsibilities they need sound planning and wholehearted cooperation of all interested groups.

I appeal, then, for your help in cooperating with government to develop a more adequate program for medical care for the aging. All states face this problem, although in Minnesota the problem is more acute than it is in states that set an arbitrary limit on medical care payments. All of our people stand to benefit by a program that would relieve them of worry about insecurity and dependency in old age.

Permit me to summarize the problem as I see it. We all agree on the goal—and on most aspects of the problem. We cannot retreat from our position of providing Old Age Assistance recipients with adequate, highest-quality medical care. We want to make sure that other senior citizens whose incomes are small, yet enough for independence as long as no extraordinary expenses are required, need not become "medical indigents" when they become ill. We want personal dignity as well as health for our later years.

Meanwhile, we know that the numbers of those over sixty-five will increase. We know that thus far voluntary commercial insurance programs have not made available to members of this group, at a moderate cost, the kind of protection they need.

The proposal to include medical and hospital care insurance under OASI benefits does offer one solution. It may not be a complete solution or the best solution. It may not be acceptable to you or to the Congress. But it would offer help to state governments —hard pressed to find ways to meet all the needs for services for which they are responsible.

Difficult as these problems are, I, for one, will never recommend curtailing medical care for our senior citizens. Rather they need better care, and they need other social services which—combined with the best of medical knowledge—will make their lives happier and more constructive. I believe that, together, government and the medical profession can work out such a program.

Can you help us to find a way to apply the voluntary health insurance principle to elderly and retired people? Can you help us to develop a program, that is within our means, to provide the kind of preventive care and attention that will make the sunset years healthier and happier? Can you help us find ways to make available to all who need it the kind of physical rehabilitation that your scientific progress has already developed?

We need this help and cooperation urgently. The people feel this need, and when they feel it badly enough, they demand that it be met. The people then say, "there ought to be a law." Yet the best solution is seldom reached in an atmosphere of urgent need or bitter controversy.

I believe that our best course in seeking the right answer is in sincere and wholehearted cooperation involving the medical profession and government as well as the people who need the services. I have had most rewarding experience in cooperating with medical leaders in fields in which we do work together—for example, in improving our program for vocational rehabilitation. I find that cooperation between government and representatives of various professions and specialists in seeking solutions to major current problems is a most effective approach.

It is certain that we must find a solution, without further delay. Certainly a society with the great resources we have in both material goods and scientific talent cannot leave the health and happiness of our senior citizens to chance. Certainly we must do all we can to make most effective use of the public expenditures we make for that purpose. I ask the help of the leaders of the medical profession in working out a program that will most adequately meet the needs of our older citizens for health and services of the highest quality. I know that government in the interest of the people must not—and cannot—avoid that responsibility.

Correction of Congenital Cardiac Defects Utilizing the Pump Oxygenator*

GILBERT S. CAMPBELL, M.D.
GLEN G. CAYLER, M.D.
WILLIAM R. RICHARDSON, M.D.
DAVID D. SNYDER, M.D.
G. RAINEY WILLIAMS, M.D.

THE INTERIOR of the human heart, the last anatomic frontier confronting the surgeon, is no longer an area inaccessible to surgical correction of congenital or acquired defects. General hypothermia was first used by Lewis[1] in 1952, to successfully close an atrial septal defect. Gibbon[2] pioneered the application of a mechanical heart and lung apparatus to cardiac surgery and in 1953, he successfully closed an atrial septal defect in an eighteen-year-old girl utilizing total cardio-respiratory bypass.

Initial Clinical Experiences at the University of Oklahoma Medical Center

The pump** utilized at The University of Minnesota Hospitals in the first 350 operations to temporarily supplant cardiac function has remained essentially unchanged, but methods for extracorporeal blood oxygenation and carbon dioxide removal were evolved with increasing experience and knowledge. The first 45 patients subjected to direct vision intracardiac operation in 1954-1955 were supported by controlled cross circulation.[3] In 1955 extracorporeal oxygenation was obtained in five patients by perfusion from a reservoir of arterialized blood[4] and in 15 patients by a biologic (dog lung) oxygenator.[5] In 1955 the University of Minnesota group introduced a simple disposable bubble oxygenator[6] which provided adequate flow and gaseous exchange. This safe and effective pump oxygenator system has since been utilized in various centers throughout the world. Because of previous experience with this type pump oxygenator, we elected to use this apparatus in our initial clinical cases. The following seven patients represent our initial clinical experience at the Children's Memorial Hospital with correction of congenital cardiac defects utilizing total cardio-pulmonary bypass.

Case Presentations

Patient Number One: A.J.A. (Wilburton, Oklahoma).

Referring Physician: C. K. Holland, Jr., M.D. (McAlester, Oklahoma).

This twelve-year-old boy was noted to have a heart murmur in the spring of 1957. There was a history of exertional dyspnea

*This paper is from Departments of Surgery and Pediatrics of the University of Oklahoma Medical Center.

**Sigmamotor Inc., 3 North Main Street, Middleport, New York.

and decreasing exercise tolerance for the past year. Physical examination revealed a somewhat underdeveloped boy with no evidence of cyanosis. There was a grade three ejection systolic murmur at the upper left sternal border and a fixed, split second sound. There was also a grade three mid-diastolic rumbling murmur maximal at the lower left sternal border. X-ray examination revealed marked increase in cardiac transverse diameter, mainly due to right ventricular enlargement. The main pulmonary artery segment was enlarged and the pulmonary vascular markings were accentuated. The electrocardiogram revealed right axis deviation, incomplete right bundle branch block, and probably right ventricular hypertrophy. In November 1958, he was admitted to Children's Memorial Hospital for cardiac catheterization. This study revealed a large left to right shunt through an atrial septal defect and anomalous pulmonary venous drainage from the right lung. Pulmonary blood flow was approximately four times the systemic blood flow and the right ventricular pressure was slightly elevated. On 1-21-59, the congenital defects were corrected under direct vision utilizing total extracorporeal circulation. The chest was entered through a bilateral anterior thoracotomy in the fourth interspace with a transverse sternotomy at that level. On opening the pericardium, the right atrium was seen to be approximately two and one-half times normal size and the pulmonary artery was much enlarged. After establishing total cardiac bypass the right atrium was opened and the defect in the atrial septum was found to be low and just posterior to the coronary sinus. There was a fair margin of atrial septal wall between the lowermost portion of the defect and the annulus of the atrio-ventricular valves. Both the right superior and right inferior pulmonary veins entered to the right of the atrial defect. The septal defect was closed with interrupted silk sutures and positioned in such a fashion as to divert the right pulmonary venous drainage into the left atrium. His immediate postoperative course was uncomplicated; however, three weeks following operation he developed "post-commissurotomy" syndrome characterized by fever, arthralgia, anorexia, and tachycardia. He responded to treatment with bedrest and salicylates and was discharged home on 3-21-59.

Patient Number Two: M. F. (Bristow, Oklahoma).

Referring Physician: D. L. McAlister, M.D. (Bristow, Oklahoma).

This five-year-old boy was first admitted to the Children's Memorial Hospital at the age of ten months because of a loud systolic murmur at the second interspace and frequent upper respiratory infections. Physical examination revealed a well-developed boy with malar flush and redness of the fingertips but no obvious cyanosis. There was a grade four stenotic systolic murmur maximal at the pulmonary area and a diminished pulmonary second sound. X-ray examination revealed slight cardiac enlargement with right ventricular contour. The pulmonary artery segment was prominent, and the pulmonary vasculature diminished. Electrocardiogram showed marked right ventricular hypertrophy and minimal right atrial hypertrophy. He was followed in our congenital heart clinic until 11-7-58, when he was admitted for cardiac catheterization which revealed pure pulmonary valvar stenosis of marked severity with a right ventricular systolic pressure of 160 mm.Hg. On 2-4-59, corrective surgery was performed utilizing cardiac bypass. The heart was exposed through a midline sternotomy incision. The pulmonary artery showed typical post-stenotic dilatation. A harsh thrill was present both over the main pulmonary artery and over the outflow tract of the right ventricle. The pulmonary valve could be palpated through the soft pulmonary artery wall. After establishing total extracorporeal bypass, the main pulmonary artery was opened, revealing a valve orifice measuring 3 mm. in diameter. One of the commissures was partially open but the other two were completely fused. Under direct vision, each of the three commissures was incised out to the valve ring. No infundibular obstruction was present. The incision in the main artery was closed with running arterial silk suture. After completion of the intracardiac procedure, the right ventricular pressure

was measured and found to be only 50 mm. Hg. Postoperatively, the patient did exceptionally well and was discharged from the hospital on 2-26-59.

Patient Number Three: R.F.T. (Fox, Oklahoma).

Referring Physician: C. E. Baker, M.D. (Oklahoma City, Oklahoma).

This seven-year-old girl was admitted to Children's Memorial Hospital on 2-17-59. A precordial murmur had been noted at the age of one and one-half years and her development had been poor with frequent upper respiratory infections and perioral cyanosis with crying. Physical examination revealed a small girl with no evidence of right to left shunting. There was a grade three stenotic murmur maximal at the pulmonary area and a diminished pulmonary second sound. X-ray examination revealed slight right ventricular enlargement and a prominent main pulmonary artery segment. The electrocardiogram showed right axis deviation and moderate right ventricular hypertrophy. Cardiac catheterization on 2-4-59, showed a right ventricular systolic pressure of 100 mm.Hg. and a mean pulmonary artery pressure of 10 mm.Hg. Angiocardiograms showed pulmonary valvar stenosis with no evidence of a right to left shunt. Corrective surgery was performed on 2-18-59. The pulmonary artery was incised so that the pulmonary valve could be visualized directly. The stenosis was completely relieved by a direct incision of the fused cusps. Following this procedure, right ventricular pressure fell to 25 mm.Hg. The patient's postoperative course was completely uneventful and she was discharged home on 3-12-59.

Patient Number Four: R.G. (Ardmore, Oklahoma).

Referring Physician: R. W. Murphy, M.D. (Ardmore, Oklahoma).

This 4½-year-old boy had partially compensated congestive heart failure and frequent bouts of severe pneumonitis. He was markedly underdeveloped and very limited in activity. Physical examination revealed a small boy with no evidence of cyanosis. Physical examination showed moderate hepatosplenomegaly, venous engorgement and tachypnea as evidence of congestive failure. He had a combined hyperdynamic cardiac impulse. There was a grade three systolic ejection murmur at the pulmonary area with a fixed, split second sound. There was also a grade three regurgitation systolic murmur at the apex which transmitted out into the axilla. X-ray examination revealed marked cardiac enlargement with a prominent pulmonary artery segment and pulmonary plethora. The electrocardiogram showed left axis deviation, incomplete right bundle branch block and combined ventricular hypertrophy. Cardiac catheterization on 2-17-59, revealed an atrial septal defect of the low or primum type and evidence of mitral regurgitation, probably due to a cleft mitral valve. On 2-25-59, surgical correction of his defects was carried out on a total cardiac bypass. The heart was exposed through a bilateral transsternal thoracotomy. On opening the pericardium the right atrium was found to be approximately three times normal size. After total extracorporeal bypass was established a right atriotomy was made and a large volume of bright red blood appeared in the operative field. This bleeding was due to regurgitation from the left ventricle through the cleft in the mitral valve and into the right atrium via the atrial defect. To facilitate repair, cardiac arrest was accomplished by cross clamping the ascending aorta. Two defects were then visualized in the atrial septum. One defect was a classical ostium primum type and measured 2 cm. in diameter. The second defect was at the foramen ovale level and measured 1 cm. in diameter. The foraman ovale defect was closed with interrupted silk sutures. The cleft in the anterior leaflet of the mitral valve was exposed and repaired through the primum defect. The primum defect was then closed with interrupted silk sutures which were tied over a strip of compressed polyvinyl sponge. The ascending aortic clamp was then released and normal sinus rhythm returned. Blood samples obtained from the superior vena cava and from the right ventricle after correction of the defects showed no residual left to right shunting. This child's postoperative

course was uneventful until 3-6-59, when he developed a pneumothorax on the right side. He responded to drainage by chest suction and antibiotics and is now ready for discharge.

Patient Number Five: V.W. (Midwest City, Oklahoma).

Referring Physician: V. M. Rutherford, M.D. (Midwest City, Oklahoma).

This nine-year-old girl was noted to have a heart murmur and anemia on a preschool examination at the age of five years. She showed poor development and had exertional dyspnea and decreased exercise tolerance. Physical examination revealed a poorly developed girl with no cyanosis. There was a combined hyperdynamic cardiac impulse. There was a grade three systolic ejection murmur at the pulmonary area with a fixed, split second sound. There was also a grade three systolic regurgitant murmur at the apex radiating out into the axilla. X-ray examination revealed marked cardiac enlargement with a prominent main pulmonary artery segment and pulmonary plethora. The electrocardiogram showed left axis deviation, incomplete right bundle branch block and combined ventricular hypertrophy. Cardiac catheterization on 2-16-59 revealed a large left to right shunt through a low atrial septal defect. A diagnosis of an ostium primum type atrial septal defect with mitral regurgitation due to a cleft mitral valve was made. On 3-4-59, an open heart operation was performed. The heart was exposed through a bilateral transsternal thoracotomy incision. The heart was markedly enlarged and had a paradoxical beat due to systolic regurgitation of blood from the left ventricle across the atrial septal defect into the right atrium. The aorta was relatively small and the pulmonary artery quite large. Operative correction of the defects was carried out in a fashion similar to that of patient number four. Blood samples from the superior vena cava and right atrium after repair showed no residual left to right shunt. This patient has had an uneventful postoperative course and is now ready for discharge.

Patient Number Six: P.S. (Oklahoma City, Oklahoma).

Referring Physician: C. F. Foster, Jr., M.D. (Oklahoma City, Oklahoma).

This six-year-old girl was first admitted to Children's Memorial Hospital on 1-25-54, at the age of one year with anascara, precordial murmur, and a hemoglobin of 4 mg.%. She responded to treatment consisting of blood transfusions, anticongestive measures, and antibiotics. A grade four systolic stenotic murmur at the upper left sternal border persisted, however, after correction of her anemia, and a diagnosis of congenital heart disease was made. She was then followed in our congenital heart clinic until 1959, when she was admitted for further cardiac studies. At this time physical examination revealed a well-developed little girl with a malar flush and red fingertips but no evidence of cyanosis. The cardiac murmur was unchanged from previous examinations. The pulmonary second sound was diminished. X-ray examination revealed slight cardiac enlargement with right ventricular contour. The main pulmonary artery segment was not remarkable and the pulmonary vasculature slightly diminished. There was a right aortic arch. On 3-3-59, cardiac catheterization and angiocardiography was performed. These studies revealed a severe infundibular and valvar pulmonary stenosis and a ventricular septal defect. The right ventricular systolic pressure was 110 mm. Hg. There was a very small right to left shunt at the ventricular level. The systemic arterial saturation was 90%. On 3-11-59, open correction of her defects was carried out utilizing the pump oxygenator. The heart was exposed through a mid-sternotomy incision and upon opening the pericardial cavity the aorta was seen to be somewhat anterior and larger than normal. The main pulmonary artery was small, measuring approximately 8 mm. in diameter. The left and right pulmonary arteries, however, were of normal size. After establishing cardiac bypass a right ventricular cardiotomy was made in the outflow tract of the right ventricle. To facilitate correction, cardiac arrest was performed by cross clamping the ascending aorta. The ventricular septal defect was closed with numerous interrupted arterial silk sutures which were tied over a compressed polyvinyl sponge. After closure

of the ventricular defect the clamp on the ascending aorta was released. No left to right shunting at the ventricular defect was noted. Cardiac rhythmicity returned to normal spontaneously. The obstructing infundibular muscle at the level of the crista supravetricularis was then excised. In order to correct the valvar stenosis cardiac arrest was again carried out and the main pulmonary artery incised. The stenotic valve was opened to the wall of the artery along its three commissures. The pulmonary artery incision was then closed with a running arterial suture. The aortic clamp was then released and normal sinus rhythm returned after a brief episode of ventricular fibrillation. Right ventricular systolic pressure after repair was 50 mm/Hg. The patient awakened immediately at the end of the procedure and her postoperative convalescence has been totally uneventful.

Patient Number Seven: S.N. (Talihina, Oklahoma).

Referring Physician: D. E. Bendingfield, M.D. (Talihina, Oklahoma).

This seven-year-old Indian girl was noted to have a heart murmur at the age of one year and had been smaller for her age than any of her six siblings. Physical examination revealed a grade three stenotic systolic murmur maximal at the pulmonary area and a diminished pulmonary second sound. There was no evidence of cyanosis. X-ray examination revealed a heart with right ventricular contour and a normal pulmonary segment. The electrocardiogram showed an indeterminate axis and moderate right ventricular hypertrophy. She was admitted to the Children's Memorial Hospital on 3-8-59, at which time a cardiac catheterization revealed valvar pulmonary stenosis with no evidence of left to right or right to left shunting. The right ventricular pressure was at systemic levels being 100 mm.Hg. On 3-18-59, open correction of the pulmonic valvar stenosis was carried out utilizing the pump oxygenator. The heart was exposed through a midline sternotomy incision. The pulmonary artery was somewhat enlarged but did not show a great deal of post-stenotic dilatation. After establishing total bypass the main pulmonary artery was opened and the pulmonary valve orifice visualized directly. It was 5 mm. in diameter. In order to minimize blood loss, cardiac arrest was established by aortic cross clamping. The stenotic valve was then opened all the way to the valve ring along its commissures. The surgeon's finger was then introduced into the outflow tract in the right ventricle through the pulmonary valve. No infundibular stenosis was present. In order to be completely sure that there was not an associated small ventricular septal defect, a right ventricular cardiotomy was performed. Excellent visualization of the ventricular septum was obtained and no defect was found. The aortic clamp was released and cardiac rhythmicity spontaneously returned to normal. Right ventricular systolic pressure after correction was only 30 mm/Hg. The patient's postoperative course thus far has been completely uneventful.

Discussion

We believe our complete lack of mortality and our very low postoperative morbidity rate is unique for a center's initial clinical experience with cardiac bypass. Our success is, in large measure, due to the previous experience of our surgical team with this technique at other centers. The work here has also been greatly facilitated by the close teamwork between the various departments and groups involved, e.g., Surgery, Medicine, Pediatrics, Radiology, Anesthesiology, the Blood Bank, and the Nursing Service. The Blood Bank group under Dr. DeWitt Hunter has provided outstanding assistance in obtaining and providing adequate quantities of very fresh blood for each procedure.

Table One summarizes our experience to date with correction of congenital heart defects by cardiac bypass techniques at the Children's Memorial Hospital. As is listed, all patients have survived their corrective procedures and as near as can be determined clinically, all have been totally corrected. The postoperative morbidity has been practically nil. No patient has had congestive heart failure, and no patient has had any significant pulmonary difficulty in the immediate postoperative period.

Table Two is a summary of our experi-

TABLE I—CLINICAL DATA AND RESULTS (0% Mortality)

Patient	Age— (Yrs.)	Weight (Pounds)	Diagnosis	Surgical Indications	Postoperative Course	Post-correction Data
1	12	76	A.S.D.2° Anomalous Drainage Rt. P.V.	Progressive Exercise Intolerance. QP/QS = 4/1	"Post-Commissurotomy" Syndrome	S.V.C. O_2 Saturation = R.V. O_2 Saturation.
2	5	46	P.S.	R.V. Sys. Pressure of 160 mm. Hg. QS unchanged with exercise	Uneventful	R.V. Sys. Pressure 50 mm. Hg.
3	7	41	P.S.	R.V. Sys. Pressure of 100 mm. Hg.	Uneventful	R.V. Sys. Pressure 25 mm. Hg.
4	4½	28	A.S.D. 1° M.R. A.S.D. 2°	Congestive Heart Failure QP/QS = 3/1	Pneumonia Pneumothorax	S.V.C. O_2 Saturation = R.V. O_2 Saturation
5	9	51	A.S.D. 1° M.R.	Decreased Exercise Tolerance. QP/QS = 4/1	Uneventful	S.V.C. O_2 Saturation = R.V. O_2 Saturation
6	6	46	P.S. V.S.D.	Sl. Dec. Exer. Tol. R.V. Sys. Pressure of 110 mm. Hg. Small R to L Shunt	Uneventful	S.V.C. O_2 Saturation = R.V. O_2 Saturation R.V. Sys. Pressure 50 mm. Hg.
7	7	46	P.S.	R.V. Sys. Pressure of 100 mm. Hg.	Uneventful	R. V. Sys. Pressure 30 mm. Hg.

Index of Abbreviations:

A.S.D. 2°	—Atrial Septal Defect, Secundum Type
A.S.D. 1°	—Atrial Septal Defect, Primum Type
M.R.	—Mitral Regurgitation
P.S.	—Pulmonary Stenosis
P.V.	—Pulmonary Veins
QP	—Pulmonary Blood Flow
QS	—Systemic Blood Flow
R.V.	—Right Ventricle
S.V.C.	—Superior Vena Cava
Sys.	—Systolic
V.S.D.	—Ventricular Septal Defect

ence with perfusion in these seven patients. The average perfusion rate has been 1850 ml/min/m^2. No postperfusion acidosis has been noted and no significant postoperative arrhythmia or heart block has occurred.

The use of an open technique is mandatory for the repair of atrial septal defects of the primum type (patients 4 and 5) and for ventricular septal defects (patient 6). Partial anomalous pulmonary venous drainage (patient 1) can be corrected by closed methods, but is done with much greater accuracy by the open method. Valvar pulmonary stenosis (patients 2, 3 and 7) can also be done satisfactorily by closed methods,[7] but we think that here also repair under direct vision is superior for most patients. The open technique also has the advantage of allowing the surgeon to deal with any unexpected complicating lesion such as infundibular stenosis or an associated ventricular septal defect.

Our choice of the cardiac bypass technique for open heart work rather than hypothermia and inflow occlusion, is based on the former technique being more versatile and allowing the surgeon a greater margin of safety if any complication should arise.

Neither techniques for surgical correction or cardiac bypass are static. The present methods are being improved and replaced constantly and certainly optimal methods have not as yet been developed. Currently we are working with a disc-type oxygenator* in the experimental laboratory at the

*Purchase of this equipment was made possible by contributions from an interested Oklahoma citizen.

TABLE II—CARDIAC BY-PASS PERFUSION DATA

Patient	B.S.A.*	Total Perfusion Time (Min.)	Total Duration Of Cardiac Arrest	Perfusion Rate (ml./min./ m2	Post-Perfusion pH	Post-Perfusion Plasma Hgb. (mgm%)	Comments
1	1.2	16	0	1500	7.31	81	Difficulty with coronary sinus suction.
2	0.8	9½	0	1800	7.46	32	No complications
3	0.8	9	0	1830	7.40	82	No complications
4	0.6	28	16 min.	1830	7.33	77	No complications
5	1.0	23	10 min.	1850	7.50	71	No complications
6	0.8	44	11 min. 19 min.	2000	7.38	75	No complications
7	0.8	17	7 min.	2060 Average 1850 ml/min/m^2	7.39	52	No complications

*Body Surface Area in Square Meters.

University of Oklahoma Medical Center. This apparatus lends itself to higher flow volumes and will prove of help for more prolonged periods of perfusion and for obtaining the increased perfusion rates required for larger patients. Techniques for making cardiac bypass safer for small children and infants are also being investigated.

Summary

The initial experiences with cardiac bypass for surgical correction of congenital heart defects at the University of Oklahoma Medical Center is presented. Corrective procedures have been accomplished in seven patients to date. There has been no operative mortality. Operative morbidity has been limited to one case of "post-commissurotomy" syndrone and one case of postoperative pneumonia and pneumothorax. Both these patients responded to appropriate therapy. Postoperative clinical evaluation shows that none of the seven patients has any significant residual defect.

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ADDENDUM

Since the submission of this report patients 4, 5, 6 and 7 have been discharged from the hospital. In addition three more patients have undergone cardiopulmonary by-pass and successful corrective surgery for (1) atrial septal defect with anomalous right pulmonary veins, (2) Tetralogy of Fallot and (3) infundibular pulmonic stenosis.

Myxoedematous Goiter Associated with Thiocyanate Intoxication*

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Omer L. Eubanks, M.D.: I should like to present to you a 53 year old married half-Indian and half-white male common laborer whose chief complaint was weakness of five weeks duration.

Present Illness: The patient was well until November, 1956, when he noted the onset of dizziness. He was told by his local doctor that he had hypertension and was treated with a liquid medication which we discovered was nitrocyanate. This contains 960 mgs. of sodium thiocyanate per ounce and 480 mgs. of potassium thiocyanate per ounce. He took this medication intermittently at first and then regularly for the six months prior to admission. He noted the onset of dyspnea on exertion and pedal edema in March of 1957, and suffered a cerebral vascular accident the following month. He had a right hemiplegia and facial weakness with dysphonia. This cleared in months with some residual weakness of the right arm and difficulty in speech. There was little change in his condition until five weeks prior to admission at the University of Oklahoma Hospitals when he became so weak and lethargic that he had to go to bed. He remained there with his symptoms progressing to the point of extreme lethargy and confusion. His wife and daughter noticed that he had a swelling on the right side of his neck below the angle of the mandible. This swelling was first intermittent, then constant and rapidly progressive. The enlargement finally spread to the anterior and left side of his neck. They also noted that he had bilateral peri-orbital edema. He denied signs of tracheal or esophageal compression, paroxysmal nocturnal dyspnea, or orthopnea. His family has noted that the patient perspired only slightly, was intolerant to cold, that he was drowsy and that his memory had decreased over the last

*Presented at the University of Oklahoma Hospital.

two years. His weight had decreased from 180 to 155 pounds and his auditory acuity had also diminished.

Past History: The patient's past history was essentially non-contributory.

Family History: There was no family history of thyroid, renal or cardiovascular disease.

Systems Review: The patient had noted a loss of libido during the last two years.

Physical Examination: Blood pressure, 120/86. Pulse, respirations, and temperature were normal. The patient appeared older than his stated age of 53 and seemed chronically ill. He was unkempt and his voice was deep and croaky. His speech was slow and hesitant. He was slightly obese, lethargic and quite pale. The skin was very dry and scaly. Axillary and chest hair was scant and the hair of the head was dry and coarse. There was also noted thinning over the lateral eyebrow region. His face was rounded and puffy with edema of the right side of the face. The lymph nodes were not remarkable. There was a marked diffuse hard enlargement of both lobes and isthmus of the thyroid. The right lobe was much larger than the left. One could not define the lower border at the sternal notch. The neck veins showed little distention, however, there were small dilated vessels in the skin overlying the gland. There was no bruit heard over the thyroid. Examination of the eyes showed only moderate atherosclerotic changes of the vessels of the fundus. The patient had decreased hearing bilaterally and carious teeth. The chest had an increased AP diameter with fair expansion. The lungs were clear to percussion and auscultation. Heart sounds were distant. The liver was palpable 3 cm. below the right costal margin. Genital and rectal examination was not remarkable. The patient was lethargic with a poor memory and slow mentation. Orientation was poor. His speech was slow, slurred and hoarse. His general knowledge was decreased and he could not do abstract thinking or understand parables. There was a right facial weakness and decreased hearing bilaterally. The uvula lifted to the left. There was generalized muscle weakness which was more marked on the right. There was some atrophy and spasticity of the right arm with a positive Hoffman reflex and hyperactive deep tendon reflexes. The right leg was slightly spastic with hyperactive deep tendon reflexes and a positive Babinski. All deep tendon reflexes showed slow return.

Admission Laboratory Data: Hemoglobin 7.5 gms. %, Hct. 21%, and 2.45 million red blood cells per cu. mm. White blood count was 4,450 per cu. mm. with 56% lymphocytes. Urinalysis showed a specific gravity of 1.020 and was unremarkable except for an occasional white blood cell. B.S.P. retention was 20% in 45 minutes, cholesterol was 383 mg. % with 172 mg. % esters. Serum calcium, 8.4 mg. % and phosphorus 2.7 mg. %, Van den Bergh, 0.6 mg. %, blood V.D.R.L., negative, total serum protein 6.5 gm. % with 4.4 gms. % albumin and 2.1 gm. % globulin. Blood urea nitrogen, alkaline phosphotase, fasting blood sugar, serum electrolytes, thymol turbidity, platelet count, bleeding, clotting and prothrombin times were all normal. An electrocardiogram showed normal QRS voltage and late inversion of the T waves. X-rays of the chest and abdomen showed no abnormality.

Hospital Course: The pertinent laboratory data during the hospitalization is given in the Table. Chronic thyroiditis or carcinoma of the thyroid was considered likely. A Vim Biegeleisen needle biopsy of the thyroid was obtained. The microscopic findings will be discussed later by Dr. Jaques. However, the impression was chronic thyroiditis. An aspiration biopsy of the bone marrow was done and it revealed a hypercellular marrow with erythroid hyperplasia. The red cells on peripheral smear were normochromic and showed some spherocytosis, polychromasia, and stippling. Blood thiocyanate concentration during the second week was 14.8 mg. %.

His hemoglobin slowly rose, the reticulocyte count remained high, serum cholesterol decreased, and the protein bound iodine remained low (Table). The patient was given no medications. By the end of the second week he was more alert and his speech was less slurred. There was no change in the

TABLE

LABORATORY DATA DURING HOSPITAL COURSE

Hosp. Week	1st	2nd	3rd	4th	5th	6th	16th*
Hbg. Gms. %	7.5	8.00		8.9	9.1	9.7	14.1
Hct. %	21	22		28	29	30	46
RBC—Million	2.45			3.45			4.86
Retic %	5.6		10.2	6.9	8.8	3.7	2.2
PBI Mcg.%	1.2		1.8	2.3	2.9	5.1	6.9
Thiocyanate Mg. %		14.8		5.9		0.8	
Cholesterol Mg. %	383	321	281	290	226	194	200
RAI %	19		65.5				65
BSP %	20			11			7
Coombs'	Neg.		Neg.				Neg.
Stools Occult Blood	Neg.	Neg.	Neg.	Neg.			Neg.
Blood Pressure	120/86	120/85	130/90	135/90	140/95	144/100	240/160

*The patient was readmitted for follow-up studies and these values are included for completeness.

size or consistency of his thyroid until the fifth week when the gland was found to be smaller and softer. At this time, the patient was voluntarily getting out of bed, talking freely, joking and taking care of his appearance. It had not been possible to obtain 24 hour urine or stool collections until the fifth week of the patient's hospitalization because of his confusion and forgetfulness. Two 24 hour urine collections for calcium obtained during the fifth week showed 10.2 mg. % (volume 725 cc.) and 7.4 mg. % (volume 750 cc.). Fecal urobilinogen obtained during the sixth week was 161.8 mg./day. His hemoglobin had risen to 9.7 gms., reticulocyte count was 3.7% and the PBI was 5.1 mgm. %. Serum cholesterol was 194 mg. % and blood thiocyanate level was 0.8 mg. %.

Henry H. Turner, M.D.: This is a very classical case of thiocyanate goiter with myxedema. The histology of the biopsy sections is quite similar to that seen in the thyroid following administration of other goitrogens. Thiocyanate inhibits the trapping of iodine by the thyroid with resulting hyperplasia. Upon removal of the inhibitor, the iodine uptake is increased, normal thyroid synthesis is restored, and the gland usually regresses to normal size. The process may be accelerated by the administration of thyroid hormone. Occasionally in goiters of long standing involution may not be complete and different morphologic alterations in the histology may be seen. In one of our patients with "iodide goiter" and which did not completely reduce in size following cessation of iodide therapy for asthma and administration of thyroid hormone, the histologic picture was that of chronic thyroiditis of the Hashimoto type. This patient's gland is rapidly regressing in size. It is firm but not hard and at present his progress is satisfactory.

Q. Is there any chance of his going over into the hyper state?

Doctor Turner: No. I see no reason for his becoming hyperthyroid.

William E. Jaques, M.D.: Examination of the needle biopsy showed thyroid and muscle tissue. The thyroid was characterized by acini lined by tall cuboidal to columnar type epithelium and by an occasional papillary excrescence. The colloid in the follicules was moderate in amount and possessed a pale

eosinophilic tinctorial quality. The interstitial tissue contained moderate amounts of chronic inflammatory cell infiltration with lymphocytes predominating. The picture is consistent with that previously described in thiocyanate goiter. Indeed, hyperplasia is the general histological picture noted when thiocyanate or, more recently, thiouracil or propothiouracil are used clinically. In these goiters, hyperplasia may be so marked that it may be mistaken for actual neoplasia. It has been stated that one well recognized pathologist had made an unequivocal diagnosis of papillary carcinoma of the thyroid gland in the first thiouracil treated thyroid that he examined. Thiocyanate goiter can be distinguished from the more common propylthiouracil goiter by the presence of more abundant but paler staining colloid.[1]

Philip C. Johnson, M.D.: Physiologically, the thyroid gland has as its function, the removing of iodides from the serum and converting them into metabolically active compounds. These compounds are then either stored or released into the serum according to the needs of other tissues. Thiocyanate goiter is a result of a temporary disruption of the first of these metabolic steps.

The thyroid gland traps iodide in concentrations approximately 25 times those found in the serum. Little is known of the biochemical steps involved in this iodide trapping mechanism. However, it is known that it requires the expenditure of energy derived from aerobic cellular metabolism.[2] The administration of adenosine has been shown to increase the iodide trap. Thyroid stimulating hormone (TSH) probably has no direct effect on the iodide trap since the administration of TSH lowers intrathyroidal iodine at the same time that it increased the serum protein bound iodine.[3]

On the other hand, many substances block or reduce the iodide trap. These include in order of potency, perchlorate, chlorate, hypochlorite, periodate, iodate, bi-iodate, and nitrates.[4] Serum concentrations of potassium thiocyanate from 4.7 to 17 mg. % were reported to be present in patients with myxedema due to a thiocyanate goiter.[5] This compares well with the value of 14.8 mg. % obtained in our patient.

Since thiocyanate blocks the trapping of iodide by the thyroid gland, we would expect the usual thyroid function tests to show, to a variable extent, decreased iodine I-131 uptake, serum protein bound iodine, and basal metabolic rates. At the same time the serum cholesterol should increase with the appearance of myxedema. This results in a relative deficiency of circulating thyroid hormone which in turn increases TSH production by the pituitary. Since the gland is now unable to trap iodide, it is unable to respond to TSH production by increasing thyroid hormone production. However, it is able to respond to this increase in serum levels of TSH by hyperplasia and production of a goiter which is deficient in stored colloid. This occurs in approximately 20% of patients treated with this drug. The simultaneous administration of thyroid in physiological doses will prevent the goiter formation since TSH production will be inhibited. Iodide administration, on the other hand, will also prevent goiters by overcoming the thiocyanate blockage directly.

Following the cessation of thiocyanate administration the blockage of the thyroid ceases. This results in a high iodine I-131 uptake for a variable period followed by a gradual increase in the serum protein bound iodine to normal. Excessive TSH production is halted, with the return to a euthyroid state following which the thyroid gland gradually shrinks to normal size. Iodine I-131 usually returns to normal at 2½ to six months.[5]

Since thiocyanate effectively blocks the iodide uptake, this drug is often used as a diagnostic and research tool. The administration of 1-2 gms. of thiocyanate orally will cause the thyroid gland to empty itself of almost all of its inorganic iodide. Thus, we have a convenient way to separate defects in trapping of iodide from defects in the steps in the production of thyroid hormones.[6] During the first two hours after iodide is absorbed into the thyroid gland, it remains as inorganic iodide which can be discharged by thiocyanate administration. If the iodide can be discharged by thiocyanate two or more hours after administration of a tracer dose, we can assume that a defect exists in

the conversion of iodide to organic compounds and not in the iodine trapping mechanism. This situation is seen in some goitrous cretins and in thyroid glands under treatment with thiouracil.[6]

In addition to a goiter and hypothyroidism, this patient has at least one other complication of thiocyanate therapy. The elevated reticulocyte count associated with anemia, and an active marrow shows that hemolysis played a significant role in the production of his anemia. That this is a complication of therapy, is suggested by the negative Coombs' and his continued increase in red blood cell count after stopping the drug.

Keith A. Klopfenstein, M.D.: Thiocyanates have received considerable attention through the years because of their wide range of pharmacological action. It was first noted by Pauli, in 1903, that they would lower blood pressure and they have been used intermittently for this purpose since that time.

Their toxic properties were recognized early, thus they were not widely used until popularized by Westphal, in 1925. They were effective in lowering blood pressure in many patients and seem to be particularly efficacious in combatting hypertensive headaches, relieving them at times without lowering blood pressure after other measures had failed.

Thiocyanates enjoyed rather widespread use in the 1930's and 40's and are used more today than is generally appreciated. As late as 1952, 14,000 pounds of thiocyanates were prescribed in the United States as medicine; and they are used more extensively abroad.[7]

Thiocyanates occur in a wide variety of plants in nature, particularly in the brassica family of plants, which includes cabbage and cauliflower. They also occur in appreciable quantities in soy bean flour. Chesney, in 1928, noted that rabbits fed on cabbage developed hyperplastic goiters, and Suk, in 1931, associated cabbage ingestion with goiter formation in humans.

Therapeutic blood levels for hypertension are said to lie between 8 and 12 mg. % with toxic concentration generally considered to be in the range of 14 mg. % or above. The toxicity is not necessarily related to the blood level and many instances of severe toxic manifestations have been reported with blood concentrations below 10 mg. %. There was one case of fatal toxicity which was said to have had blood concentrations of only 3.3 mg. %.

The excretion of thiocyanates varies by as much as 600 to 800% among individuals, therefore, blood concentrations must be followed closely when it is used therapeutically. The therapeutic dose ranges from 60 to 720 mg. per day. Toxic manifestations are quite numerous; one of the most noteworthy being its action on the thyroid. Beamish and others have shown that the effect on blood pressure is not secondary to hypothyroidism, as thiocyanate is effective if patients are maintained on iodine or thyroid hormone while under therapy.[8] The glands in thiocyanate goiter are typically hyperplastic, but exhaustion atrophy has been reported by McGavack and others with prolonged thiocyanate therapy.[9] Thyroiditis has also been reported in association with thiocyanate therapy, with fever and acute enlargement of the gland. Less acute, prolonged tenderness and swelling of the gland has also been reported.[10] Involution of the gland may take months and the prior condition of the gland is rarely attained on withdrawal of thiocyanates. Thyrotoxicosis may occur when sufficient amounts of iodide are given to overcome thiocyanate block. Thyrotoxicosis is commonly seen in rabbits withdrawn from thiocyanate and they also may develop exopthalmus. In man, exopthalmus has also been reported in association with thiocyanate goiter.

Central nervous system disturbances are common as manifestations of thiocyanate intoxication. They include lethargy, depression, psychosis with hallucinations, nervousness, irritability and a decrease in mental acuity, hearing and vision. These symptoms are probably due, in part, to the hypothyroid state, but may also be secondary to a direct action of thiocyanate on the central nervous system. It has been shown that thiocyanate can be converted to cyanide in the erythro-

cytes and a significantly toxic concentration of cyanide in the blood has been observed with the therapeutic use of thiocyanate.[11,12] Cyanide produces histotoxic anoxia by interfering with the cytochromoxidase. This may account for some of the effects of thiocyanate.

There are several reports of hemiplegia occurring in patients with a high blood concentration of thiocyanate. It has been felt that these were probably associated with hypotensive episodes. Gastrointestinal disturbances are also common, with nausea, vomiting and diarrhea frequently seen. Thiocyanate causes a decrease in gastric secretion, both in volume and in acid content, which is said to be resistant to histamine stimulation. Various types of dermatitis have been noted; the usual one being a papular rash quite similar to that seen with sensitivity to bromides. Exfoliative dermatitis has been reported in patients under thiocyanate therapy. Osteoporosis also occurs associated with an increased urinary excretion of calcium.

Thiocyanates have been thought by some to decrease adrenal function. Healy described three patients in 1931, who developed mucosal and skin pigmentations with shock and coma quite similar to that seen in adrenal crisis. It has also been reported that there is a decrease in adrenal lipid content in post mortem specimens following thiocyanate therapy. Sheps and Beamish, in 1956, measured adrenal function in a series of patients on thiocyanate therapy and could find no measurable decrease in adrenal functions.[13]

Anemia, which may be quite severe, is a common complication of thiocyanate therapy, but has received very little attention in the literature. Beichert and Jorke, in Germany, gave high doses of thiocyanates to dogs over a prolonged period and found that they developed normochromic, normocytic anemia.[14] This anemia was believed to be due to an erythrostatic effect with an arrest in the bone marrow at the level of the basophilic normoblast. They also noted groups of cells in the bone marrow that resembled the megaloblasts seen in pernicious anemia. The anemia in dogs was associated with a low reticulocyte count, normal red blood cell fragility, a normal serum iron, and a serum bilirubin. These same workers have also reported the use of potassium thiocyanate in the therapy of primary polycythemia with successful remissions associated with a fall in hemoglobin and hematocrit to normal levels.[15] This fall is also associated with a decrease in reticulocyte count and decreased erythroid activity in the bone marrow. In their patients, the urine urobilinogen and the indirect-acting fraction of the Van den Bergh reaction were noted to be elevated. It was their impression that there was probably a hemolytic component associated with the fall in hemoglobin as well as a bone marrow depression.

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MEDICAL CENTER

Problem of Massive Upper GI Hemorrhage With Emphasis on Peptic Ulcer

FRANK H. HOWARD, JR., M.D.

A 1956 graduate of the University of Oklahoma School of Medicine, Frank H. Howard, Jr., M.D., is now serving a residency in General Surgery at the University of Oklahoma Medical Center. He is a member of Phi Beta Kappa and Alpha Omega Alpha.

MASSIVE upper gastrointestinal hemorrhage from peptic ulcer disease is a very serious, and often fatal, disease. To date, there is still no ideal method of treatment. For this reason the hospital records of patients with this disease were reviewed for the ten year period from 1948 through 1957.

During this period there were ninety-four patients admitted to the University of Oklahoma Hospital who were diagnosed as having massive upper gastrointestinal hemorrhage. Only patients who met specific criteria, as shown in Table I, were considered as massive bleeders.

The source of the hemorrhage is recorded in Table II. Patients with terminal leukemia and uremia were specifically omitted. The results in this Table are similar to those reported by others.[1]

Of the ninety-four patients in this group, sixty patients were bleeding from peptic ulcer disease. Their treatment followed one of three methods: 1. medical therapy alone, 2. medical therapy followed by elective gastric resection during the same hospital admission, or 3. emergency operation. Twenty-

This paper is from the Department of Surgery, University of Oklahoma Medical Center, Oklahoma City, Oklahoma and was presented at the Fourth Interne-Resident day, May 23, 1958, sponsored by the Office of Post Graduate Education of the University of Oklahoma Medical Center. It was selected as a prize winning essay by the Oklahoma Chapter of the American College of Surgeons, and presented at the Sequoyah meeting, September 6, 1958.

TABLE I

Criteria of Massive Upper Gastrointestinal Hemorrhage
1. Admission hemoglobin of 7 gms. % or less
2. 3,000,000 RBC's or less
3. In clinical shock
4. Require 2,500 cc. blood or more during the hospital stay.

three patients were treated with medical therapy alone with a mortality of 21.8% (Table III). Another twenty-three patients initially were treated medically followed by elective gastric resection with a mortality of 13.0%. Thirteen patients had emergency gastric resections with 23.1% mortality. The last patient in the group was not included in any of the above categories because he expired soon after admission before any form of therapy could be administered.

Fifty patients in the group with peptic ulcer disease were bleeding from a duodenal ulcer. Nineteen of these patients were treated medically with a mortality of 5.3%. Twenty patients were treated medically followed by elective surgery with 10% mortality. Ten patients had emergency operation with 20% mortality. The over-all mortality of this group was 12% (See Table IV).

TABLE II

Etiology of Massive Upper G.I. Bleeding From 1948 to 1957

Etiology	Total Number	Percent of Total
Peptic ulcer:		
Duodenal ulcer	50	53.2%
Gastric ulcer	9	9.6%
Stomal ulcer	1	1.0%
Unknown	15	15.9%
Esophageal varices from cirrhosis	12	12.8%
Carcinoma of stomach	1	1.0%
Lymphosarcoma of stomach	1	1.0%
Rupture of aneurysm of hepatic artery into roux-y limb of choledochojejunostomy	1	1.0%
Hypertrophic gastritis	1	1.0%
Post-infectious mononucleosis hepatitis	1	1.0%
Banti's syndrome esophageal varices	2	2.1%
TOTAL	94	100.0%

TABLE III

Therapy of Patients Bleeding From Peptic Ulcer Disease From 1948 through 1957.

Therapy	Number of Patients	Number of Deaths	Mortality Percentage
Medical alone	23	5	21.8
Medical followed by elective operation	23	3	13.0
Emergency operation	13	3	23.1
Patient expired before any therapy	1	1	
TOTAL	60	12	20.0

There were nine patients in this group with peptic ulcer disease who had gastric lesions, four of whom were treated medically and died. Three patients were treated medically followed by elective gastric resection with one death, and two had emergency gastric resections with one death. The over-all mortality was 66.6% (See Table V).

Discussion

Upper gastrointestinal hemorrhage may occur anywhere from the ligament of Treitz to the oral cavity. The most common sites are in the first part of the duodenum, the stomach and the lower one-third of the esophagus. The symptoms presented by these patients were: hematemesis, melena, shock, or any combination of the three.

TABLE IV

Therapy of Patients Bleeding From Duodenal Ulcers From 1948 through 1957

Therapy	Number of Patients	Number of Deaths	Mortality Percentage
Medical alone	19	1	5.3
Medical followed by elective operation	20	2	10.0
Emergency operation	10	2	20.0
Patient expired before any therapy	1	1	
TOTAL	50	6	12.0

The diagnosis of upper gastrointestinal hemorrhage may be made in several ways. If a patient has a history of vomiting blood, it is almost certain the hemorrhage is from the upper gastrointestinal tract. If a patient presents with a history of melena or passage of red blood per rectum, it is im-

TABLE V

Therapy of Patients Bleeding From Peptic Gastric Ulcers From 1948 through 1957.

Therapy	Number of Patients	Number of Deaths	Mortality Percentage
Medical alone	4	4	100.0
Medical followed by elective operation	3	1	33.3
Emergency operation	2	1	20.0
TOTAL	9	6	66.6

possible to diagnose bleeding from the upper gastrointestinal tract without additional information. If a tube can be introduced into the stomach and blood aspirated, or if a string is swallowed and returns stained with blood, there is strong evidence to support the diagnosis of upper gastrointestinal bleeding provided the bleeding has not been stimulated in the nasopharynx by passage of the tube or string. If a patient has melena or bleeding per rectum, a tentative diagnosis of upper gastrointestinal hemorrhage can be made only if a disease known to cause upper gastrointestinal bleeding is evident.

It is of utmost importance to be able to determine the exact cause and source of gastrointestinal hemorrhage for this may determine the type of therapy to be administered. A careful history and physical examination will frequently differentiate between peptic ulcer disease and esophageal varices. In every case an appropriate hematologic survey should be made to rule out bleeding due to a blood dyscrasia. Upper gastrointestinal examination with contrast media is an important aid and in some hands has an 80% accuracy in demonstrating esophageal varices or peptic ulcer.

TABLE VI

Etiology of Hemorrhage in Patients with Cirrhosis and Massive Upper G.I. Hemorrhage. (3)

Etiology	Percentage of Total
Esophageal varices	59.2
Gastric varices	2.6
Peptic Ulcers	18.4
Gastric Erosions	5.3
Hiatus Hernia	1.3
Undetermined	3.9
No Cause Found	9.2

Bromsulphalein retention studies are of considerable value in establishing whether or not the patient has cirrhosis of the liver with esophageal varices. Fifteen per cent bromsulphalein retention, or greater, is considered by some[2] to be the dividing line between patients with cirrhosis and those without. This figure, unfortunately, is not completely reliable. It should be stated, however, that a patient with proven cirrhosis and massive gastrointestinal bleeding is not necessarily bleeding from esophageal varices. Fainer and Halstead[3] reviewed seventy-six case histories of patients with Laennec's cirrhosis and massive upper gastrointestinal hemorrhage and found various causes for the hemorrhage as indicated in Table VI.

The treatment of patients with massive upper gastrointestinal hemorrhage from peptic ulcer disease falls into three main categories, as previously mentioned: medical management only, medical management followed by elective gastric resection, and emergency operation. Some[4,5] advocate one or the other of the above three categories of treatment to the exclusion of the others. They maintain that all patients should be treated similarly. It is not the purpose of this paper to state what is the best form of management for these patients. However, in our opinion, it is unrealistic to employ only one form of management. There were several patients in this series who were bleeding from an ulcer that had eroded into the wall of a large artery who might have died had they been treated by medical management alone. On the other hand, some patients will stop bleeding under medical management alone and, accordingly, need not be subjected to the risk of an emergency laparotomy and gastric resection. One look at the mortality rates of massive upper gastrointestinal hemorrhage by any form of therapy indicates there is no perfect way to manage this problem. Each patient should be evaluated individually. If surgical treatment is selected as the method of treatment, certain facts should be considered. An elective operation carries a considerably lower mortality rate than an emergency one—13% as compared with 23.1% respectively in this institution. For this reason, it behooves one to try to control the hemorrhage

TABLE VII

Criteria for Emergency Operation (6)

1. Rapid exsanguinating hemorrhage.
2. Any patient who continues to bleed for more than 48 hours while receiving medical management.
3. Any patient in whom a stable hematocrit can't be maintained by 500 ml. of blood per 8 hours.
4. Any patient over 50 years of age.
5. Any patient whose bleeding stops and then recurs while on medical management.

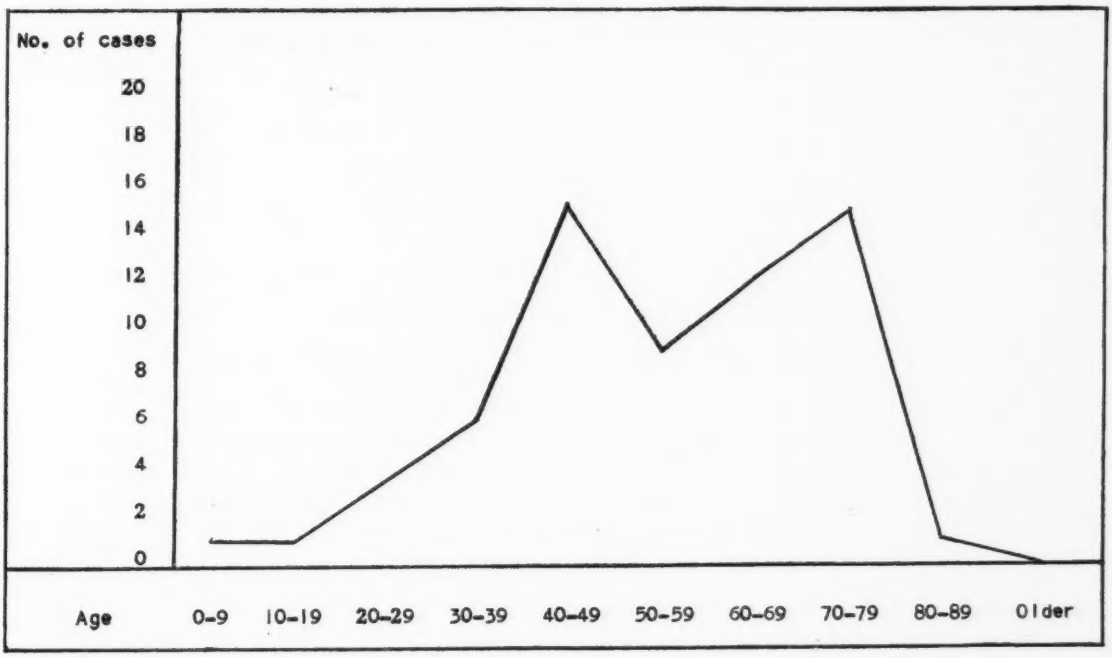
conservatively and to perform elective operations rather than emergency ones. Conversely, it is important not to continue conservative therapy in the face of continuing hemorrhage. With continued bleeding, operation should be carried out within the first forty-eight hours, or sooner, since the mortality rate climbs rapidly the longer it is postponed. Kirtley[6] recommends emergency operation for the criteria as shown in Table VII.

In evaluating a patient, two important factors should influence the decision for early or emergency operation. The first is massive hemorrhage from gastric lesions. In our experience during the past ten years there were nine such cases. Four were treated medically with four fatalities. Three were treated conservatively followed by elective operation with one death; two had emergency operation with one death. The over-all mortality was 66.6%. These cases are too few to be statistically significant, but corroborate other reports[7] in the literature concerning the prognosis for hemorrhage from gastric lesions. Therefore, early emergency operation should be elected more frequently when the source of massive upper intestinal bleeding is from a gastric ulcer.

The second important factor that should influence the decision for early or emergency operation is age. Smythe[2] states, "There is no medical contraindication to surgery in severe continuing hemorrhage in a patient with an anatomical lesion amenable to surgery. In elderly patients, in whom one is

TABLE VIII

Age incidence of 60 patients with massive hemorrhage from peptic ulcer disease



most tempted to try a conservative approach, this may be dangerous. The factors which make one reluctant to operate also enhance the risk of delay. Vascular insufficiency of heart, brain, and kidneys may constitute an indication for early surgery rather than a contraindication." In the present series of cases the over-all mortality for massive hemorrhage from peptic ulcer disease was 17.4% for patients under fifty years of age and rose to 24.5% for patients over sixty years of age (Table VIII). In reviewing the mortality rates of such a series of patients, it is, therefore, quite important to know the age incidence as well as the number who were bleeding from gastric peptic ulcers.

Summary and Conclusions

Over the ten year period 1948 through 1957, sixty patients were admitted to the University of Oklahoma Hospitals with the diagnosis of massive upper gastrointestinal hemorrhage from peptic ulcer disease. All of these patients were treated by one of three methods: medically alone with a mortality rate of 21.8%; medically followed by elective gastric resection with a mortality rate of 13.0%; or emergency operation of 23.1%. The over-all mortality for the entire group was 20.0%. Bleeding from a gastric ulcer, or from a peptic ulcer of the duodenum after the fifth decade, is associated with a much higher mortality rate—66% and 24% respectively.

Because there is still no ideal way to treat such patients, each patient must be evaluated individually to determine the best form of therapy. Two factors which indicate early or emergency operation are hemorrhage in the aged and hemorrhage in patients with gastric ulcer.

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$125,866 RESEARCH GRANT has been awarded Robert H. Bayley, M.D., Professor of Medicine and Heart Station Director, for continuation of studies using new electronic computer techniques in measurement of the electrical field produced by the heart beat. National Heart Institute approved the grant for a five-year period.

MEDICAL-SURGICAL CONFERENCE

PHEOCHROMOCYTOMA

RENE MENGUY, M.D., Ph.D., and MRS. ESTHER COMPTON

Proceedings of a weekly conference sponsored by the Medical and Surgical Services, VA Hospital and the Departments of Medicine and Surgery, University of Oklahoma School of Medicine.

Doctor Camp: The patient is a 68-year-old, white male who was admitted here on August 14, 1958. He had been complaining of palpitations, occasionally blurred vision with some headache and dizziness for about a year. His local physician had treated him for hypertension with some white pills which we later found out to be phenobarbital. The patient thought that he improved somewhat after this. His past history is interesting. In 1918, shortly after his discharge from the service, he was diagnosed as being schizophrenic and from that time until the present he has been in many institutions all over the country. His sister mentioned that he had been hypertensive since his discharge from the service but there is no record available of this. In 1954 the patient was admitted here with a left-sided pleural effusion which proved to be grossly bloody. Extensive workup was done at that time to find out whether or not the patient had tuberculosis and he was actually started on a specific treatment for tuberculosis with streptomycin and PAS. However, all cultures and guinea pig inoculations eventually proved to be negative. During the latter part of that hospital stay he developed congestive heart failure and he was digitalized. He responded to this treatment very well. At that time, his blood pressure ranged between 200 and 240 systolic over 120 diastolic. His urinary workup showed nothing abnormal. He ceased taking digitalis when he left the hospital and since then he has had no more symptoms of congestive failure. From 1955 to 1958 he was relatively asymptomatic. On this admission his blood pressure was 250 systolic over 140 diastolic with a regular pulse of 104. The pertinent findings on physical examination were Grade III hypertensive fundi with several hemorrhages and old exudates. There was cardiomegaly and a Grade II systolic murmur was heard over the apex. The neurological examination was normal except for the patient's mental status which was compatible with a diagnosis of schizophrenia. The relevant laboratory workup was as follows: The WBC was within normal range with a normal differential. The hemoglobin was 14 grams with 47% hematocrit. The blood electrolytes were normal. Urinalysis showed a concentration of 1.010 to 1.012 with 2+ to 4+albuminuria. A urine culture was positive for E.coli. This organism proved to be sensitive to chloramphenicol. A glucose tolerance test was done. His fasting blood sugar was 95 MG./100 ML. At one hour he

went up to 248 and at the end of four hours was down to 200. A diagnostic workup for the possibility of a pheochromocytoma was done. The Regitine test was markedly positive with a drop of 40 mm. systolic and 40 mm. diastolic following the intravenous injection of 5 mg. It was suggested that he be given 10 mg. and this was done. Immediately following the injection his blood pressure fell to 118/74. The patient developed a right-sided hemiplegia which lasted for 24 hours and gradually disappeared. The intravenous injection of 400 mg. of tetraethylammoniumchloride produced a fall in blood pressure. Urinary catecholamines were assayed and were abnormally high. His blood pressure ranged from 230 to 280 and he never had any episodes of flushing or sweating. The patient was prepared for operation on the 24th of last month. He was given 200 mg. of cortisone preceding operation. During the operation blood pressure determinations were done from minute to minute. During palpation of the right adrenal gland there was a significant rise in blood pressure which went from 160/100 to 220/140. There was no response on palpation of the left adrenal gland. The right adrenal gland was removed. During anesthetic induction there were no complications. The patient did not need to have Levophed during his operation nor was it necessary to use Regitine during the procedure. Postoperatively his course was not so benign. On the 3rd post operative day he became febrile. Blood cultures were obtained and the patient was started on chloramphenicol, penicillin and streptomycin. The blood pressure today was 230/160.

Doctor Ridings: The chest film at this time is clear to any abnormality. The excretory urogram shows no abnormalities on either side. No masses are seen around the kidneys either on this film or on the scout film of the abdomen.

Dr. Hammarsten: This patient brings up several problems. One that always troubles us on the Medical Service is which patient with hypertension should be tested for the possibility of a pheochromocytoma, and then which tests are going to be the most helpful. Doctor Conrad, would you comment on the tests done on this patient, the biological tests in general, and the possibility of actual determinations of pressor amines in the urine.

Doctor Conrad: In regard to what type of patient should be selected for a Regitine test, I think that a good rule is that every patient who has hypertension or presents himself with a history of hypertension should be considered as a possible case of pheochromocytoma. Ordinarily, patients with this condition are younger than this patient and therefore, I think that you should be more vigorous in your search for pheochromocytoma in the younger patients. Certainly there seem to be fewer patients with pheochromocytoma who have a labile type of blood pressure. Most cases which are reported now are patients who have a fixed hypertension. Occasionally, as this patient presents, there will be evidence of severe retinopathy with pheochromocytoma, so that the presence of retinopathy per se does not rule out the possibility of a pheochromocytoma.

Regitine has proved the most useful of the agents used for the bedside diagnosis of pheochromocytoma. There are two circumstances in which the Regitine test will give a false positive result. First, which is the most common occurrence, is the patient with uremia. In uremic patients a fall in blood pressure following the administration of Regitine can occur in the absence of a pheochromocytoma. Another possible circumstance in which a false positive test may occur is in a patient who has received barbiturates. These patients will also respond occasionally with a fall in blood pressure to the administration of Regitine. Occasionally, the results of the test will vary somewhat according to the proportions of norepinephrine and epinephrine secreted by the tumor. When the tumor is secreting a large proportion of epinephrine the administration of Regitine may cause an immediate drop in pressure; whereas if the proportions of epinephrine secreted is small then Regitine will not give as sudden a fall in blood pressure.

There are other interesting facts about pheochromocytomas. First, it is surprising

that a number of these patients have hypotension. Upon assuming an upright position the patients will have a drop of blood pressure. I don't know with what frequency this phenomenom occurs but it has been reported as being a manifestation occurring in pheochromocytomas. The other interesting feature of pheochromocytoma is the regularity with which these patients show an increased oxygen uptake and increased metabolic rate, which may be sometimes very high, i.e., from 135 to 150 per cent. At the same time the patients show an elevation of body temperature with a rectal temperature that is consistently a degree or two above normal. During hypertensive crises the extremities become pale and sweaty, the skin temperature will fall. I think the only other comment I will make at the present time about patients with pheochromocytoma is that the cause of death of these patients is very often pulmonary edema. It is not known whether this acute pulmonary edema is associated with or due to acute temporary left ventricular failure or due to some effect of the circulating pressor substances or the pulmonary capillaries. Cyanosis and pulmonary edema are the most frequent causes of death.

Doctor Hammarsten: Would you comment on the usefulness of the biological test as opposed to the chemical determinations and also on the tetraethylammoniumchloride test which the patient had.

Doctor Conrad: I don't know too much about biological tests except how they are performing them here. Apparently everyone here is satisfied with their use. Regarding assays for pressor amines in the urine, I know that pressor substances can be demonstrated in the urine which do not necessarily reflect increased production by an adrenal medullary tumor. I would presume that false positive tests can be obtained although apparently the people who are using the tests here don't feel that way about it. I have no personal experience with the chemical determinations in the urine but along this line one might say that there are instances where levels of catecholamines in the urine have been found without pheochromocytoma. These patients as a rule have been patients with an anxiety state. The concentrations of catecholamines in the urine although increased, did not approach levels ordinarily seen in patients with pheochromocytoma.

The tetraethylammoniumchloride test is more valuable in other instances of hypertension than in pheochromocytoma. The object of doing the test is in trying to differentiate between renal causes of hypertension and essential hypertension, the difference being that, when there is a renal cause for the hypertension, the circulating substances apparently produced by the kidney cannot be blocked by the use of ganglionic blocking agent and the hypertension will persist even though the ganglionic block is obtained with tetraethylammoniumchloride. The patient with essential hypertension will show a prompt fall in blood pressure as tetraethylammoniumchloride is given and a ganglionic block is produced. This is a neat way of trying to distinguish between renal and essential hypertension. The only exceptions to this rule are patients with chronic renal disease, late in the stage of renal disease.

Another comment which may be made at this point is that adrenal medullary tumors are not necessary for the production of the pheochromocytoma syndrome. Ganglionic tissue which can be responsible for hypertension is distributed anywhere in the body and can be found any place in the abdomen, in the thorax and cases have been recorded where a functioning tumor was discovered intracranially.

Q. Would you comment on the cold pressor test and its value in the workup of a patient with pheochromocytoma?

Doctor Conrad: The cold pressor test has been used ordinarily in patients who have essential hypertension or who have a predeliction for hypertension. These patients will show a satisfactory early response to the cold pressor test. In such patients the cold pressor response is greater than the response obtained by administration of some provocative agent for pheochromocytoma like histamine. In patients with a pheochromocytoma with a normal blood pressure at

the time of the test, the cold pressor test is usually exceeded by the response to the provocative test by histamine. I don't believe that the cold pressor test is of any help in the clinical examination of patients with labile or fixed hypertension due to pheochromocytoma.

Doctor Hodges: I was particularly interested in Doctor Conrad's statement that orthostatic hypotension is one of the manifestations of pheochromocytoma. Unfortunately, this patient has not been out of bed for many years, so that it is difficult to get a good idea about this symptom. On two or three occasions in which we tried to get him up post-operatively this did occur. The reason he hasn't been up more since operation is because he has phlebitis in the area of the cutdown on his leg.

Prior to operation, I was very much in favor of having air studies done on him so that we would know whether there was more than one tumor. Certainly, from what is presented here it seemed very likely that this patient had at least one tumor, and possibly had tumors on both sides. The significance of this was of course that we would have to be prepared for removal of both adrenal glands. Aortography was not done because there has been a death reported after aortography in a patient with pheochromocytoma. This case report was interpreted by the writer as being a very definite contraindication of aortography in any case of pheochromocytoma. I don't know for certain how he arrived at these conclusions because the autopsy showed actual rupture of the tumor, and the author surmised that the injection of the contrast media stimulated the outpouring of a great deal of norepinephrine or whatever substance was being secreted and that this was sufficient to rupture the tumor with the patient's demise from hemorrhage. In view of such a report one should be reluctant to perform aortography. Since the medical workup was quite definite we didn't feel that this risk had to be taken. However, in view of the subsequent developments, I do wish that we had known what the inside of the renal arteries looked like. We palpated them at operation and were not able to make anything specific except that they were quite hard and one can't tell from a hard artery whether it's obstructed inside or whether it's merely calcified. However, we did make a very thorough examination of the abdomen and as has been related already, the only time that we produced an actual rise in blood pressure was during palpation of the right adrenal gland. Both adrenal glands were visualized and no tumor was found in either of them. Because of this response on the right side the right adrenal gland was entirely removed. The pathological examination shows no sign of any tumor or hyperfunctioning medullary tissue. We palpated the aorta up to the diaphragm as well as along the vena cava. We also examined the root of the mesentery and every other location suggested where a tumor might be. Since the operation the patient continues to behave like a patient with a pheochromocytoma. The blood pressure now fluctuates very widely at different intervals throughout the day with no known cause. We are now wondering if there is still a possibility of his having such a tumor in the mediastinum. We feel fairly certain that it is not in the abdomen.

Doctor Campbell: For those of you who are interested in reading further about this problem, there is a good review article in the November 1957 issue of the *"Journal of Chronic Diseases."*[1] Now I would like to go over a couple of brief points. The clinical syndrome was first reported in 1886 by Frankel and in 1927 the first time that anyone operated on a patient who had a retroperitoneal tumor resulting in hypertension was Doctor C. H. Mayo. The patient's retroperitoneal tumor was removed and the blood pressure returned to normal. As you know, Doctor Grace Roth, of the Mayo Clinic was the first to use histamine in trying to produce an attack in the patients with pheochromocytoma and she has had a long and continued interest in this field. Doctor Roth is in the operating room at all times when patients at the Mayo Clinic are being explored for a pheochromocytoma. It is sometimes a little discouraging to find in how many varied locations the chromaffin tissue may be because it has been reported in the heart, the testes, liver, kidney and

other sites. One favorite hiding place that Doctor Hodges looked for is the origin of the superior mesenteric artery. Tumors vary in weight from 5 up to 2,000 gms. The age variation is also very wide; pheochromocytomas have been removed from a patient five months of age and from a patient as old as 81 years. However, 90% of the tumors are present in the adrenal gland and it seems to be more frequent in the right adrenal than the left. Approximately 16% of the tumors are bilateral, and approximately 8% of them are malignant. A case report published in the Scandinavian literature gives an idea of the difficulty encountered in finding some of these tumors. The patient was operated on nine times unsuccessfully; finally the tumor was found up behind the liver in the area of the inferior vena cava. It is very important to have Regitine in the operating room when the patient is being explored for a tumor. Palpation of the tumor can produce severe hypertension and as much as 25 mg. of Regitine in divided doses may be necessary to keep the pressure at fairly normal levels. Following the operative procedure, the big problem if a tumor has been removed, is one of severe hypotension. This can be managed by norepinephrine. Doctor Conrad mentioned that one of the possible causes of death in patients with this disorder is acute pulmonary edema. This may be the basis of acute backward heart failure due to severe systemic vosoconstriction and hypertension.

Doctor Menguy: When one operates upon a patient suspected of having this condition one is reminded of operation for hyperparathyroidism, for hyperinsulinism or for Cushing's disease. The surgeon operating on patients with such conditions is working on mere circumstantial evidence. There is no radiological, or palpable evidence of a tumor. Therefore, one has to undertake operation that is often of an extremely major nature with no objective evidence of the lesion. Therefore one should not undertake the surgical treatment of a patient with a suspected pheochromocytoma very lightly. One should proceed only on extremely secure grounds with all the laboratory tests that we have at our disposal. I would have liked to have seen a provocative test with histamine in this patient since he does have a labile type of blood pressure. Speaking of laboratory tests, there is a chemical test that can be used in this condition. This test was first used by Von Euler and consists in the assay of catecholamines or epinephrine-like substance in the blood. The original method was extremely unwieldly and difficult. This method has been modified and simplified by Doctor William Manger[2] and the test as used at the Mayo Clinic can be run by technicians. Normally there are about three to five micrograms per liter of epinephrine-like substances in the blood. In a patient with pheochromocytoma the levels are higher than six micrograms per liter. As far as I recall, in normal control patients no levels higher than five micrograms were found and I do not recall there being any false positives. In a patient with a labile type of blood pressure the assay for these epinephrine-like substances can be done in blood drawn at a time of an attack produced by injection of histamine. I think that the future of diagnosis in pheochromocytomas lies in this method.

Regarding air studies, I think they are useless in patients with pheochromocytomas. The risk of producing a very severe hypertensive crisis by manipulation incident to the air study is always present. The attack, of course, could be controlled by Regitine If there exists good evidence for the diagnosis, one does not have to know on which side the tumor is present because exploration is done through the abdomen. The problem is different from that of Cushing's Disease in which, due to the patient's obesity, the exploration has to be conducted through one flank. Therefore, in such conditions, it may be useful to know on which side the tumor is on.

Incidentally, a good method for finding which side the tumor is present is simply to palpate the abdomen and the flanks. Very often, especially when the tumor is of a significant size, a hypertensive crisis can be produced by palpation of the side of the abdomen on which the tumor is located. Occasionally a pheochromocytoma may be revealed in a patient in which it was unsuspected previously when exploratory laporo-

tomy is done for some other condition. Manipulation or contraction of the abdomen incident to induction of anesthesia will produce a very severe hypertensive crisis. This should make one suspect a pheochromocytoma.

Doctor Campbell has touched on the hypotension following removal of the adrenal tumor. This is a phenomenon common to all endocrine tumors. Removal of a functioning tumor results in a temporary depression of the function of that particular tumor. Temporary diabetes occurs following the removal of an islet cell tumor, tetany follows the removal of parathyroid tumor and acute cortical insufficiency is produced by the removal of an adrenocortical tumor. Simularly, when one removes a pheochromocytoma a dramatic fall in blood pressure occurs. This must be controlled by the administration of Levophed. In this regard, it has been found that patients having been treated by hypertensive drugs such as Arphonad are temporarily resistant to Levophed. Therefore, if a patient is to be operated on for pheochromocytoma, one must make sure that he has been off such drugs for at least one to two weeks.

These tumors have one peculiarity, in that histologically it is impossible to tell whether they are malignant or benign. Only recurrence of symptoms following removal of the primary tumor will tell if that tumor was malignant. One other interesting point that may be mentioned is that almost never are these patients obese. Due to their hypermetabolism the vast majority of them are thin or at a fairly normal weight level for their size.

Doctor Woods: I would like to say a few words about the assay of pressor substances in the blood. An acquaintance of mine, Doctor McC. Goodall, at Duke, has worked for several years assaying catecholamines in blood and urine. He has used a biological assay which has the advantage of differentiating epinephrine from norepinephrine. The importance of this lies in the well known fact that tumors may vary in the relative amounts of epinephrine and norepinephrine secreted. Therefore, in a case in which the tumor is secreting nothing but norepinephrine, you would expect to find bradycardia rather than tachycardia. You would also not expect to find any great change in glucose metabolism. The pheochromocytomas which produce mainly norepinephrine are the ones which, in general, produce the plateau type of hypertension, while those secreting mainly epinephrine produce paroxysmal hypertension.

Regarding the assay of pressor substances in the blood, we have felt that the fluorometric methods used for this assay are not reliable enough, at least as regards the assay in the blood where the levels are low. The fluorometric assay seems to be more reliable in the urine where the concentration is higher. In our experience the 24-hour secretion of pressor amines was not above 200 micrograms in cases of essential hypertension. In cases of pheochromocytoma the 24-hour levels started generally about 400 in 24 hours and went up over 2,000 micrograms.

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ABSTRACTS

Cardiovascular Reactions to Symbolic Stimuli

STEWART WOLF.*

Circulation, 18: 287-292, August, 1958

Much of the confusion concerning the role of life stress in disease derives from failure to distinguish between cause and mechanism. All mechanisms are per force organic and at the same time functional, since they involve the functions of units of the body's equipment. Causes, on the other hand, are likely to derive from the outside, often from noxious stimuli in the environment. The causes, which may be multiple, activate the pathogenic mechanisms and produce bodily disorders and disease. The ability of symbolic stresses to participate in the activation of disease mechanisms depends upon the fact that most bodily organs are connected with and responsive to impulses reaching them via autonomic and endocrine pathways from the highest integrative centers of the nervous system, the interpretive areas of the brain. The cardiovascular apparatus is no exception to this generalization and it was therefore possible to document the effects of stress on the rate and rhythm of the heart, the pattern of the electrocardiogram, hemodynamic mechanisms, the mechanisms responsible for renal blood flow, and blood flow through other viscera. There is also evidence that reactions to life stress enter into the mechanism which determines the level of circulating cholesterol and serum lipids. These reactions were formulated into a theory which was propounded as the physiologic response "as if". It was pointed out that most individuals who see a cinder in the eye of another begin themselves to lacrimate as if there were a cinder in their own eye. A hungry person who sees or even thinks about a delicious meal may salivate and may indeed pour forth increased amounts of gastric juice. Another example of the physiologic response "as if" was observed in the study of cardiac output in response to exercise. It soon became evident that it was unnecessary to exercise the subjects in order to induce the characteristic hemodynamic adjustments. They could readily be called forth by the mere discussion of exercise. A possible "as if" response to explain increased serum lipids during psychological stress included the assumption that lipids are mobilized into the blood to meet demands for unusual muscular effort. There is some evidence from treadmill and other studies that this is true. Perhaps the coronary-prone individual sees the challenges in his life figuratively in terms of burdens, and therefore he adapts physiologically as if unusual muscular effort were involved and calls forth a high concentration of lipids into the blood stream. At the present time, of course, such an inference is purely speculative but it may stimulate productive efforts along new directions in research.

*Professor of Medicine.

A New Anastomotic Approach to Radical Left Colectomy Preliminary Report

G. M. BROWN, Jr.,* and T. A. BYRD.**

The American Surgeon, 24: 141-147, 1958

A new anastomotic approach to radical left colectomy in a series of twelve dogs has been presented. The basis of this approach is a reversal of flow of bowel contents from left colon to right. Its satisfactory function has been observed in dogs over varying periods of from two to ten months. All surviving dogs have maintained their preoperative weight or have gained weight. Gross anatomic and roentgenogram changes have been discussed and examples presented.

If absorptive studies on this problem prove as satisfactory as the physical and clinical studies, this procedure may present an adjunctive method of unrestricted left colectomy. By allowing restoration of bowel continuity, this procedure can extend the scope of resection, irrespective of individual physical or anatomic variants.

*Visiting lecturer in the Department of Surgery, University of Oklahoma School of Medicine.

**Doctor of veterinary medicine.

Evaluation of a Method for Detecting And Following Urinary Tract Infection in Females Without Catheterization

HARRIS D. RILEY, JR.*

The Journal of Laboratory and Clinical Medicine, 52: 840-848, December, 1958

In order to avoid the hazards of bladder catheterization, a method of collecting urine for culture in females by means of a clean voided technique was investigated. A comparison of 81 pairs of catheterized and voided urine specimens from 42 female patients, 34 of whom had paralytic poliomyelitis and eight with no evidence of urologic disease or conditions predisposing to urinary tract infection, was made. Comparison of these paired samples from the same individual according to the species and number of bacteria isolated revealed that satisfactory urine specimens for culture can be obtained by the voided technique. When used in conjunction with colony counts or gram-stained smears of the urine, it is an adequate method of detecting significant bacteriuria in females. It is a particularly valuable procedure for screening for urinary tract infection, especially in patients predisposed to urinary infection, and in whom catheterization is almost certain to produce urinary infection. The risks inherent in bladder catheterization should not be neglected and its use restricted to situations in which it is clearly indicated. To establish an accurate diagnosis of urinary tract infection determination of the number of bacteria present in the urine is as important as their identification.

*Professor of Pediatrics.

Determination of Magnesium In Erythrocytes

RAUL CARUBELLI,* WILLIAM O. SMITH,** and JAMES F. HAMMARSTEN.***

J. Lab. and Clin. Med. 51: 964-976, June, 1958

Magnesium deficiency as the cause for clinical syndrome in man has been reported by several groups of investigators but has not been universally accepted. It is true, for instance, that not all patients with delerium tremens have a low serum magnesium concentration. It is also true that some patients without symptoms of magnesium deficiency may have a low serum value.

It has been postulated that the intracellular fluid magnesium level would be a better guide to a body deficit than the extracellular fluid (serum) level and might correlate more closely to clinical symptomatology. This appears reasonable when one considers that magnesium is primarily an intracellular cation and exerts its biological effects mostly within the cells.

Accordingly, a technique for measuring intracellular magnesium concentrations has been developed. Measurement is made on erythrocytes since these are the only readily accessible cells. The technique consists of the spectrophotometric titration of magnesium with EDTA after removal of iron by combination with potassium thiocyanate and extraction with isoamyl alcohol. Recovery studies proved most satisfactory.

Erythrocyte magnesium concentration has been measured on 13 healthy adults. The mean value is 5.29 $\pm$ 0.34 mEq./L. with a normal (2 S.D.) range of 4.61 — 5.97 mEq./L. Studies on disease states, principally delerium tremens and uremia, are underway.

*Biochemist and Research Associate of the Biochemistry Section, Oklahoma Medical Research Foundation.

**Assistant Professor of Medicine, University of Oklahoma School of Medicine; Assistant Chief Radiosotope Service, Veterans Administration Hospital.

***Associate Professor of Medicine, University of Oklahoma School of Medicine; Chief Medical Service, Veterans Administration Hospital.

Necrobiosis Lipoidica Diabeticorum

JAMES W. KELLEY.*

Plastic and Reconstructive Surgery, 22: 342-347, October, 1958

Necrobiosis lipoidica diabeticorum has always been considered a medical or dermatological problem. In 1951, however, Cawley and Dingman reported a case successfully treated with radical excision and skin grafting. The plastic surgery literature fails to make mention of this disease or its treatment. Therefore it was thought advisable to present this review of the existing literature and to report another case successfully treated with radical excision and skin grafting so that others may possibly benefit from these observations.

*Instructor, Department of Surgery, University of Oklahoma School of Medicine.

Urinary Tract Infection in Paralytic Poliomyelitis

HARRIS D. RILEY, JR.,* and VERNON KNIGHT.**

Medicine, 37: 281-297, December, 1958

The development and course of urinary tract infection has been described in 44 of 50 nearly consecutive cases of paralytic poliomyelitis. The disease is characterized by its indolence, frequent lack of urinary symptoms, persistence, and steady progression in the severely disabled patients. Bladder catheterization and immobilization are important influences in the development of urinary tract infection. Treatment is only slightly effective. A presumed result of frequent use of antimicrobial drugs is a high predominance of B. proteus and A. aerogenes in cultures of urine. Urolithiasis was present in 21 of the 44 patients with urinary tract infection.

Twenty per cent of the patients exhibited persistent diastolic hypertension, which appeared to result from some effect of poliomyelitis other than renal damage by infection.

*Professor of Pediatrics.

**Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

Requirements of Mn^{++} and Co^{++} for the Synthesis of Ascorbic Acid by Liver Extracts Of Animals Deprived of Tocopherol

RANWEL CAPUTTO,* PAUL B. McCAY,** and MARY P. CARPENTER.***

The Journal of Biological Chemistry, 233: 1025-1029, November, 1958

Enzyme preparations from livers of vitamin E-deficient rats and rabbits synthesized 70 to 90 per cent less ascorbic acid than preparations from control animals. The effect was observed after feeding diets with a low content of tocopherol from two to twenty days at which time the experiments were terminated. Addition of Mn^{++} increased synthesis 315 per cent in preparations from deficient animals but had no effect on preparations from controls. Co^{++} produced increases of 278 per cent and 35 per cent in deficient and control preparations, respectively. Ethylenediaminetetraacetate activated the preparations from deficient animals 480 per cent but had no effect on control animal systems.

Determination of Mn^{++}, Ca^{++}, and Mg^{++} in the livers disclosed no differences between control and deficient animals. Total Fe and Fe^{++} ions were slightly diminished. The findings suggested that in tocopherol deficiency the states of some metal ions are altered, causing them to function less efficiently.

*Associate Professor of Research Biochemistry, University of Oklahoma School of Medicine, and Head of Department of Biochemistry, Oklahoma Medical Research Foundation.

**Instructor in Research Physiology, University of Oklahoma School of Medicine, and Assistant Head of Department of Biochemistry, Oklahoma Medical Research Foundation.

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Two New Faculty Members

New names on the faculty roster of the University of Oklahoma School of Medicine include Ollie Boyde Houchin, Ph.D., assistant professor of research biochemistry and Marjorie S. Keele, M.D., instructor in pediatrics.

Their appointments were recently approved by Regents of the University of Oklahoma.

Doctor Houchin was an instructor in pharmacology at the Medical Center from 1942 to 1944. He returned last fall to join the staff of the oncology section of the Oklahoma Medical Research Foundation.

HOUCHIN

The biochemist holds an M.A. from the University of Missouri. He then studied at Yale University one year before completing work for his doctorate at State University of Iowa.

After leaving the Medical School here in 1944, he was assistant professor of biological chemistry at Loyola University Medical School, Chicago; assistant professor of biochemistry and pharmacology at University of Louisville Medical School; assistant professor of chemistry at Denver University, and, from 1951 to 1958, assistant professor of medicine and neurology at the University of Arkansas School of Medicine, Little Rock.

Current research includes studies of the biochemical nature of schizophrenia and the effect of parathormone and citrate on magnesium deposits in bone.

KEELE

Doctor Keele was an instructor in the Department of Pediatrics of Southwestern Medical College, Dallas, for two years before coming to Oklahoma City.

She received her M.S. at North Texas State College, Denton, and her M.D. at Southwestern in 1949. After interning at Parkland Hospital in Dallas, she served a pediatric residency at Children's Medical Center, Dallas, from 1950-53, and was chief resident and teaching fellow for one year of that period. Later she was a pediatric cardiology fellow at the University of Minnesota.

Woods Awarded Clinical Investigatorship

Alexander H. Woods, M.D., a new instructor in medicine at the University of Oklahoma School of Medicine and physician on the Veterans Hospital staff, has been awarded a Veterans Administration clinical investigatorship, one of a dozen such grants given nationally this year.

He came to the Medical Center from Duke University Medical School, where he was a U. S. Public Health Service post-doctoral research fellow in biochemistry the past two years.

WOODS

The three year clinical investigator appointment will give him an opportunity to devote more time to research he has started in the following fields: transplantation of living tissues; immune reactions as a cause of disease; cancer therapy.

Doctor Woods received his bachelor of science degree in biochemistry at Harvard; his M.D., at Johns Hopkins Medical school. He interned at Johns Hopkins Hospital and took residencies in medicine at Duke Hospital and the Durham, N.C., Veterans Hospital.

He was an instructor in medicine at Duke from 1955 to 1956 and later served as acting chief of hematology at the Durham hospital, attending physician and consultant in the medical outpatient clinic.

PRESIDENT'S LETTER

In review of the past year under the present administration, we cannot say that any of our major problems of organized medicine have been completely solved, or that they will ever be, but in all fields we believe that significant gains have been made and that the dignity of your Medical Association has continued to grow. These accomplishments have not been the result of any one individual, but the fine cooperative effort of your committees, governing body, and the county medical societies all working together as a team.

As we look toward the future, the one thing that stands out as the most important tool of Organized Medicine—in which the Oklahoma State Medical Association is a part—is unity, willing cooperation, adherence to a code of ethics, and constant striving to improve medical care for our patients. Your new president and officers for 1959-60 need this kind of support, and with it you can be sure of excellent leadership.

I would like to express my sincere gratitude to all of you for the privilege of serving this past year as your President. I have had the finest committees, council and staff that any president could ever hope for. Cooperation has been most inspiring from beginning to end, and to all of these men I owe a special vote of thanks. For any success that we can claim, these men deserve the credit. As for myself, I feel that I have been the most richly rewarded.

E. C. Mohler, M.D.

E. C. MOHLER, M.D.
President

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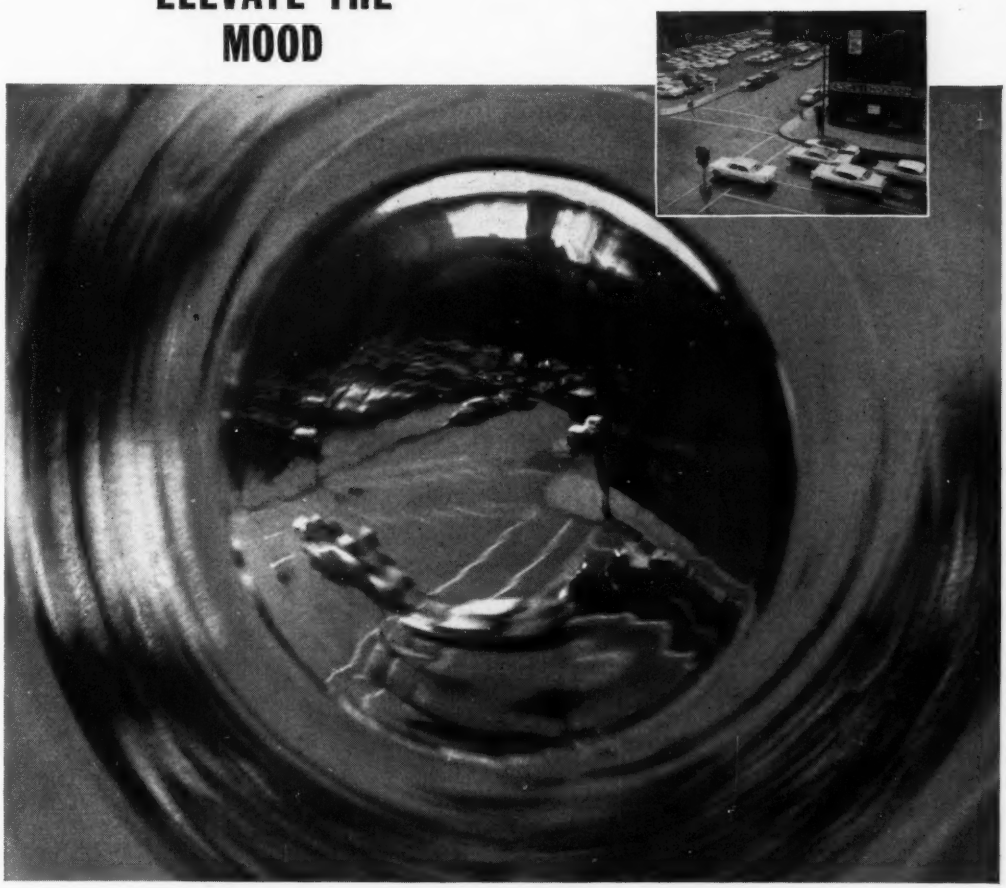

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*Pratt, R. T. C., and McKenzie, W.: Anxiety States Following Vestibular Disorders, Lancet *2*:347 (Aug. 16) 1958.

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Research in the Service of Medicine **SEARLE**

Special Articles

FIFTY YEARS OF MEDICAL GENETICS

The union of biochemistry and genetics offers a rational approach to diagnosis, prevention, and therapy.

LAURENCE H. SNYDER, Sc.D.

Laurence H. Snyder, Sc. D., President of the University of Hawaii, received his doctorate from Harvard in 1926. He has held national presidencies in the American Association for the Advancement of Science, the Genetics Society of America, the American Society of Human Genetics, and Phi Sigma. Before going to Hawaii, he was Dean of the Graduate College at Oklahoma University.

Doctor Snyder also holds memberships in Phi Beta Kappa, Sigma Xi, Alpha Epsilon Delta and Phi Kappa Phi.

This article is based on Doctor Snyder's AAAS presidential address, which was given on December 28, 1958, during the Washington, D.C., meeting.

FIFTY YEARS ago, in 1908, Sir Archibald E. Garrod, presented in England a most remarkable set of Croonian lectures,[1] setting forth a new concept of human disease, which he called "inborn errors of metabolism." Garrod was far ahead of his time in this concept, and it took many years for geneticists to appreciate the full significance of his contribution. The rapid and widespread development of medical genetics at the present time owes its inception to the recently renewed interest of human geneticists in Garrod's demonstration that, through mutation, the dysfunction of a gene-controlled enzyme necessary for normal metabolism is a basic mechanism in the production of genetic disease.

The term "genetic disease" is used in this paper to apply broadly to any deviation from the usual or normal condition, for which a genetic basis can be established. I shall attempt to show that there are reasons for believing that genetics is involved in one way or another in the development of all disease.

Garrod illustrated his concepts with his own basic studies of four human anomalies: albinism, alcaptonuria, cystinuria and pentosuria. Today, both in experimental organisms and in man himself, the identification of many enzyme dysfunctions with mutant genes has reached a high point of development. On this 50th anniversary of Garrod's basic contribution, it is with deep appreciation of his foresight and ability that I offer a survey and critique of some of the advances in medical genetics that we have been able to build on the foundation of his fundamental concepts. Through the expansion of these concepts, genetics and biochemistry are rapidly becoming facets of one and the same science, and the resulting mosaic is playing an indispensible role in the progress of medicine.

The reawakening of the interest of medical geneticists in the biochemical backgrounds of genetic diseases apparently had to await the occurrence of a number of other developments.[2] Three main events brought into sharp focus the steps intervening be-

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tween the presence of a gene in the cell and the appearance of a trait or disease in the individual, and thus led to a renewed interest in Garrod's suggestions. The first of these events was the firm establishment of the concept that all metabolism proceeds through series of small sequential steps, each step catalyzed by an enzyme. The second was the demonstration[3] that increase in radiation level can increase the mutation rate. The third event was the realization[4] that with the aid of radiation-induced mutations the biochemical activities of genes can be definitively studied in microorganisms which are peculiarly suited both to genetic and biochemical investigation. The researches undertaken all over the world along these lines have brilliantly demonstrated the facts that many enzyme dysfunctions are indeed referable to specific mutant genes and that it is reasonable to presume that the production of normal enzymes is dependent on the activity of the normal unmutated alleles of these mutant genes.

Metabolic Blocks

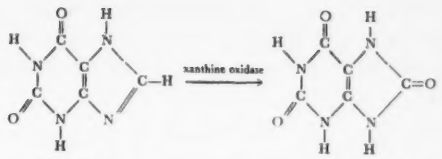
Theoretically, we may conceive of a number of ways in which the lack, or partial lack, or inhibition of an enzyme may lead to altered metabolism, and thus, perhaps, to pathological consequences. I shall present some of these possibilities in simplified form, adding examples from genetic pathology in man where they are known or suspected.

Consider the sequential reaction

$$P \rightarrow Q \rightarrow R \rightarrow S \rightarrow T$$

in which each arrow represents an enzyme catalyzing the conversion of one substance to another. The specificity of each enzyme is considered to be the result of the activity of a single gene.

As an illustrative example of what is meant by a conversion catalyzed by one enzyme, xanthine (one of the purines) is oxidized to uric acid by the enzyme xanthine oxidase. The uric acid is then excreted in the urine. In the reaction shown in Fig. 1, note the essential similarity of xanthine and uric acid, and the addition of an oxygen atom brought about by the activity of the enzyme.



Xanthine Uric Acid

Fig. 1. Oxidation of xanthine to uric acid

Returning to the sequential reaction

$$P \rightarrow Q \rightarrow R \rightarrow S \rightarrow T$$

consider now the gene that controls the enzyme that converts R to S. As a consequence of mutation, the mutant form of this gene may result in a somewhat different molecule, no longer enzymatically effective in facilitating the reaction, or at least no longer as effective as it formerly was. One likely consequence of the metabolic block is that substance R will accumulate.

$$P \rightarrow Q \rightarrow \begin{matrix} R \\ R \\ R \\ R \\ R \end{matrix} \dashv\!\rightarrow (S) \rightarrow (T)$$

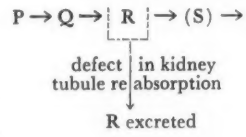
(The letters in parentheses indicate that the substance is no longer produced, or is produced in diminished amounts.)

The mere accumulation and storage of R may lead to pathological consequences. A probable example in man is Nieman-Pick disease, in which the genetic failure to degrade sphingomyelin causes this lipid to accumulate in the reticular and other cells, resulting in the manifold symptoms of the disease. A similar genetic failure to degrade one of the gangliosides leads to the storage of this lipid in the ganglion cells, with the resulting syndrome of infantile amaurotic idiocy.[5] The recent discovery of a new phospholipid, malignolipin, found only in malignant tumors and never in normal tissues, may, if confirmed, eventually place cancer in this category.[6]

Another possibility is that the accumulation of substance R may lead to its being excreted from the body. The excretion may be accompanied by symptoms, as stone formation, hematuria, and frequent micturition, in the disease xanthinuria, in which xanthine is not oxidized to uric acid.[7] Conceivably the excretion could lead to pathological consequences by depletion of R or its pre-

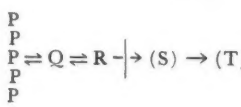
cursors, or of other substances involved in the metabolism. In the last analysis, diabetes may well prove to belong in this general category.

It should be mentioned in passing that there is a genetic disturbance of quite a different sort that can also lead to excess excretion, in the urine, of a substance normally found there only in minute amounts, if at all. This disturbance is not a block in the direct metabolism of the substance excreted, but is rather a defect in the renal tubular reabsorption mechanism for that substance.



The precise genic action involved is as yet unspecified, but the phenomenon occurs in such diseases as glycinuria, cystinuria, and renal glycosuria.[8,9]

If the reaction P → Q → R is reversible, substance P rather than substance R may accumulate, leading to disease.

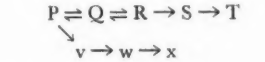


One type of glycogen disease of the liver is an excellent example, in which the genetic dysfunction of glucose-6-phosphatase prevents the reconversion of glycogen to glucose, but at a point several steps removed from glycogen itself; the reversible nature of the rest of the reaction results in the accumulation of glycogen.[10,11]

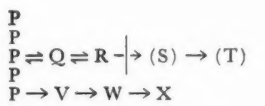
In some instances the mere absence of substance T may characterize the trait. Albinism, for example, is the result of the absence of melanin, due to the genetic dysfunction of tyrosinase. When this enzyme is lacking, tyrosine is not oxidized to dihydroxyphenylalanine, which latter substance normally proceeds through various conversions to melanin. Apparently the tyrosine is then metabolized through alternative pathways, with no further noticeable effects.

Alternative Pathways

Alternative metabolic pathways are not unusual in biochemical conversions, and this fact presents further possibilities in the production of genetic disease. It may be, for example, that although the bulk of substance P proceeds through Q, R, and S to T, some small amount of it normally passes through the steps P → v → w → x.

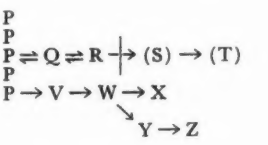


(The small letters are used to indicate that lesser amounts of substance P ordinarily follow this path.) If, then, the metabolic break occurs as before between R and S, and if substance P is thus accumulated, much more of it may be forced through this alternative pathway, and increased amounts of V, W, or X may cause pathologic effects through the altered patterns of substances in the cells.



An example in human genetics is the severe mental disease phenylketonuria, in which phenylalanine cannot be oxidized to tyrosine, and as a result passes in large amounts through deaminating reactions which certainly derange the amino acid balance in the cells.[12]

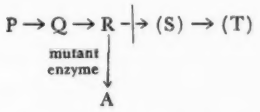
When a substance is forced through an alternative metabolic pathway, still other possibilities are opened up. When large amounts of W, for example, are available, some of this substance may in turn be diverted to a series of conversions not ordinarily followed: W → Y → Z.



Under such circumstances, Z may conceivably cause pathological effects. No example in man has been clearly established, but the development of the abnormal form of the glycolipid kerasin in Gaucher's disease may be due to a reaction of this nature. The pigments laid down in ochronosis and causing degenerative osteoarthritis in some but not all patients suffering from alcaptonuria

could well be examples of this type of genetic pathological development.

Finally, the mutant gene may result not merely in the lack of the enzyme formerly produced, but in the presence of a demonstrably functional but somewhat different enzyme. We have become aware of the fact that when the gene responsible for an *antigen* mutates, a specific but different antigen usually results from the activity of the mutant gene. It is probable that a similar phenomenon occurs in mutations involving enzymes.



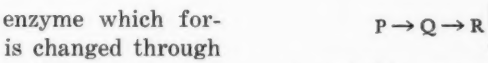
If, for example, the enzyme which formerly converted R to S is changed through mutation in such a way that it now converts R to A (a new substance), the presence of A may give rise to pathological consequences. The ten or more variant forms of hemoglobin,[13] each of which may result in a greater or lesser degree of anemia, are instances of this type of genetic disease. Sickle hemoglobin, for example, differs from normal hemoglobin in *only one* of the nearly 300 amino acid units of the half molecule, one of the glutamic acid residues of normal hemoglobin being replaced by a valine residue in the sickle form.[14] In this instance the enzyme controlled by the mutant gene accounts for a very slight alteration of amino acid sequence in the polypeptide chain. Even this alteration, however, is sufficient to cause the illness and subsequent death of those individuals having only this type of hemoglobin.

Inhibitors

In addition to the foregoing suggestions, which deal primarily with enzyme lacks that are dependent on recessive mutations in genes which normally produce functional enzymes, one other possibility should be mentioned. It is known that enzymes may be interfered with by inhibition, and it seems likely that the inhibitor may at times be a substance produced by a mutant gene which is not itself directly concerned with the development of the enzyme inhibited. Since the inhibition appears to be caused by an active, effective substance, we tend to think of genetic inhibitors in terms of *dominant* mutations which result in specific substances causing metabolic blocks.

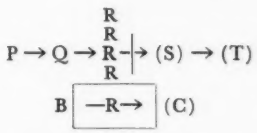
While it is certainly conceivable that the production of an effective substance could in some instances be contingent upon the homozygous state of a recessive gene, most genes seem to be capable in single dose of elaborating reasonably adequate amounts of the substances, and are thus in some degree dominant to their alleles which fail to produce the active agents.

In the reaction below, the action of the inhibitors is indicated by a box around the enzyme.



A probable example in medical genetics is the inhibition of the enzyme enolase in glycolysis, resulting in the disease hereditary spherocytosis.[15]

Many complications may be envisaged in regard to inhibitions of enzymes. To cite just one of these, it is known that excesses of certain normal metabolites may act as inhibitors. In the reaction below, the mere accumulation of substance R as a result of the genetic dysfunction of the enzyme converting R to S may cause inhibition of the enzyme converting B to C.



An example in man is the greatly reduced pigmentation which occurs incidentally in individuals suffering from the severe mental disease phenylketonuria. The excess of phenylalanine, which is found in those who have this disease, has been shown to act as an inhibitor of tyrosinase, thus deminishing the conversion of tyrosine to melanin.[16]

The foregoing series of reactions portrays in very simplified form some of the possible paths by which mutations resulting in enzyme dysfunctions may lead to genetic disease. An important underlying principle in

these concepts is that once a gene has mutated, the mutant allele is henceforth copied in its altered chemical form just as faithfully as the unmutated gene was formerly copied in its original chemical structure, thereby leading to the incorporation of the new allele into the pool of genes of the species.

Environmental Effects

The metabolic blocks thus far discussed have a direct relation to the production of genetic disease. The relation, however, may not always be so direct, and the pathological consequences of a gene may manifest themselves only in specific environmental situations. It has recently been shown, for example, that a genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase may cause an alteration in glutathione metabolism, resulting in an instability of reduced glutathione.[17] As a consequence of this instability, the red blood cells are liable to hemolysis following the ingestion of certain drugs such as naphthalene, primaquinine, sulfanilamide, and nitrofurantoin. Thus an induced hemolytic anemia develops, which, though appearing to be environmentally produced, has a definite genetic basis. From a practical standpoint, an assay of blood cells for this enzyme may make it possible to detect those individuals who are drug-sensitive and would be harmed by these drugs.

There are innumerable potential interactions between hereditary and environmental influences. It should be kept in mind that not all inhibitors are under genetic control. In addition it should be recalled that many enzymes have a coenzyme, or prosthetic group, as a necessary adjunct to the protein core. Although the protein core is determined by a gene, the coenzyme is often of vitamin origin, and is thus, in man, at least, environmentally conditioned. It is conceivable, therefore, that an enzyme which in one individual in inhibited by a geneticallly produced substance may in another individual be inhibited by an environmentally provided agent. Similarly, an enzyme which in one person is rendered dysfunctional by a genetic defect of the protein core, or apoenzyme, may in another person be inactivated by an environmental lack of the coenzyme. As a result of these and other exogenous effects, "phenocopies" may be produced, mimicking the genetic conditions. For example, nutritional siderosis appears to be a phenocopy of genetic hemochromatosis.

For many years I have predicted to my classes in medical genetics that the vitamin-deficiency diseases resulting from the nutritional lack of coenzymes would someday be found to be paralleled by similar diseases due to genetic deficiencies of the corresponding apoenzymes. This prediction has recently been fulfilled by the recognition of a genetic form of pellagra, designated as Hartnup disease.[18] Classic pellagra is, of course, the result of a nutritional absence of the coenzyme containing niacinamide. In the genetic form there is apparently a dysfunction of the corresponding apoenzyme involved in the metabolism of tryptophan. We may look forward to similar descriptions of genetic forms of scurvy, beriberi, and the rest. A genetic form of rickets, resistant to vitamin D and exhibiting hypophosphatasia, has been observed occasionally and is the subject of a careful recent study.[19] There is some evidence that it may prove to belong in the category of diseases resulting from a genetic defect in the renal tubular reabsorption mechanism, in this instance for phosphate.

Of course, the very fact that man requires vitamins in his diet in the first place is the result of gene-controlled enzyme dysfunctions apparently shared by all human beings. Most animals, for example, can synthesize L-ascorbic acid, by a series of steps, from D-glucose, and hence do not require ascorbic acid in their diets. Man and other primates, however, lack one enzyme in the series, and as a result are unable to accomplish the conversion of L-gulonolactone to L-ascorbic acid.[20] Ascorbic acid thus becomes a vitamin for man: vitamin C.

In spite of the fact that genes are normally identical from cell to cell of the individual, the cytoplasmic constituents of the cells need not be equivalent. The unequal distribution, during mitosis, of mitochondria, microsomes, and other inclusions can

result in the occurrence of identical genes in cytoplasmic environments, which differ in concentrations of enzymes, substrates, and other materials from tissue to tissue. It is well known that the effect of a gene can be altered considerably by the environment, without any change taking place in the gene itself. In this way a given gene may produce an effect in one tissue and not in another.

In like manner, one gene may exert its influence at an early stage of the development of the individual while another may not be effective until a later stage. The consequences of the gene that conditions congenital ichthyosis, for example, are clearly detectable in the embryo, while the effects of the gene for Huntington's chorea are apparent only in later life. The explanation for this phenomenon appears to rest on a firm biochemical basis. Enzymes often compete for the same substrate. Equilibria in reversible reactions require time to be achieved, and the establishment of an equilibrium may free a substrate for a new conversion by a different enzyme. The accumulation of by-products may slowly reach critical levels at which the by-products may act as new substrates or as inhibitors.

Moreover, a biological protein is a mixed population of molecules of very different ages, some being very new, while others may be months old. Correlated with these differences in age are differences in the conformation of the molecules, involving such things as the formation of dithio bonds and the substitution of amino acids.[21]

The descendents of a gene, then, may well be located in environments in the mature individual which are biochemically different from those in which the gene occurred in the embryo or the young organism. The effects of genic action could thus be quite understandably different at various times in the life history of a given individual.

It would seem to be a reasonable inference that genes do not exert absolute control over the presence or absence of specific enzymes but rather determine the potential development of particular enzymes and enzyme systems in particular environmental situations.[22]

Thus the interlocking network of hereditary and environmental influences, which has long been obvious in the overt manifestations of traits and characteristics, is now seen to be equally operative in the basic biochemical and physiological processes of the cell itself.

Dominance

The concepts which I have discussed up to this point have an important bearing on our understanding of many Mendelian phenomena which were originally but vaguely understood. In particular, such terms as dominance, recessiveness, and epistasis have become clarified in the light of biochemical considerations.[22]

In Mendel's original paper appears the statement (translated) " . . .those characters which are transmitted entire, or almost unchanged in the hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the *dominant*, and those which become latent in the process *recessive*." Since Mendel's day these terms have been applied to the genes (Mendel's *elements*) themselves as well as to the characters.

For many years the fact that one gene of a pair may be dominant to the other was merely stated, not explained. Today a simple, reasonable explanation is possible in terms of biochemical activity. The primary action of a gene appears to be the control of the specificity of a substance such as an enzyme which is responsible for the catalysis of a particular step in the synthesis or degradation of some compound. A recessive mutation in a gene often results in the failure of the mutant gene to develop the enzyme.

Albinism in man has been shown to be dependent upon the homozygous condition of a gene which has been named *c*. Thus *cc* individuals are albinos, but both *CC* and *Cc* persons are normally pigmented. Gene *C* is thus said to be dominant to its allele *c*.

The enzyme tyrosinase is always identifiable in pigmented individuals, who have the gene *C*, but is not demonstrable in al-

binos, who lack this gene.[23] It would appear that *C* is responsible for the elaboration of tyrosinase, while its mutant allele *c* fails to to develop this enzyme. It is equally apparent that one dose of *C* is grossly as effective as two. This latter fact is not surprising when it is realized that enzymes function by facilitating biochemical conversions all out of proportion to the amount of enzyme present. Since a particle of enzyme, once its quantum of catalytic action has been accomplished, dissociates itself from the resulting compound and is available for further catalytic activity, it is apparent that a small amount of enzyme may be sufficient to accomplish complete or nearly complete conversion.

It is logical to infer, then, that within a given genetic milieu one dose of *C* in a heterozygous *(Cc)* individual can elaborate sufficient tyrosinase to convert the available tyrosine to melanin. Since two doses of the gene *(CC)* could accomplish no more than this, the genotype *Cc* is as effective as the genotype *CC* in the development of melanin, and *C* is said to be "dominant" to *c*.

Consider your vitamin intake as an analogy. If, in your childhood, each of your two parents had provided you every day with your vitamin requirements, you might have had more than your minimum needs, but you would not have suffered from vitamin-deficiency diseases. If only one of your parents had supplied your needs, you would also have been free from deficiency symptoms. But if neither parent had provided any vitamins, the effects of the deprivation would have become manifest.

In man it has been demonstrated by means of phenylalanine tolerance tests that about half of the phenylalanine-oxidizing enzyme is in an inactive or ineffective form in those who are heterozygous for the gene for phenylketonuria.[24] Thus those who are carriers of the gene may be identified by a chemical test, even though outwardly they are quite normal. Other instances of genetic disease must be studied along these lines in order to test the general validity of this principle. Among the diseases, in addition to those already mentioned, in which the enzyme lack or deficiency has been specifically identified, and which are available for such study, are acatalasemia, alcaptonuria, constitutional hepatic dysfunction, at least one form of cretinism, galactosemia, several forms of glycogen disease, hypophosphatasia, and one form of methemoglobinuria.[11,25]

In addition to behaving as obvious enzymes, the substances controlled by genes may in some instances act as antigens or inhibitors or hormones. It is tempting to postulate that the activities of even these substances may be but specialized forms of enzymatic activity.

In the case of antigens, where identification is made relatively simple by the ability of the substance to provoke the production of specific antibodies, the mutation of a gene responsible for an antigen nearly always results in the development of a different but equally specific antigen. Herterozygotes are thus readily recognizable by the use of appropriate antiserums, and dominance disappears.

Between instances with no dominance and those with apparently complete dominance are all grades of the phenomenon. By means of various biochemical or immunological tests, and sometimes merely by keen observation, it is becoming increasingly possible to identify heterozygotes[23,26] and thus to move both genetic prognosis and preventive medicine from a statistical to an individual basis. It is reasonable to presume that eventually, by appropriate, though often subtle tests, all heterozygotes will be identifiable. This, too, is an area of research that offers many challenges.

Sequential Reactions

The occurrence of mutant individuals and the genetic study of these individuals and their families have on several occasions indicated the complex sequential enzymatic nature of a reaction originally supposed to be simple and direct. Conversely, the prior biochemical demonstration that a conversion involves several enzymes acting sequentially has suggested the possibility of several genetic types of a particular disease.

As an example of the first of these two principles I may call attention to the recent

work on the blood-clotting mechanism.[27] No longer can we accept the simple Morawitz theory of blood coagulation, in which it was assumed that prothrombin plus thromboplastin plus calcium ions results in thrombin, and that thrombin plus fibrinogen results in fibrin, which produces the clot. No longer can we automatically classify as hemophilia any genetic hemorrhagic disease with prolonged clotting time. The study of mutant individuals with bleeding disease has indicated that at least nine gene-controlled substances (presumably enzymes) are required for the thromboplastic conversion of prothrombin to thrombin, and that each of these trace proteins may become dysfunctional through mutation.

The superficially similar diseases involving the thromboplastic activity of the blood-clotting mechanism now include, in addition to classical hemophilia, Christmas disease, parahemophilia, deuterohemophilia, tetartohemophilia, SPCA deficiency disease, Hageman deficiency disease, Stuart deficiency disease, and factor X deficiency disease.

The second principle, involving the indication on biochemical grounds that genetically diverse forms of a disease may be expected to occur, is well illustrated in nonendemic cretinism with goiter. When the complex sequential enzymatic steps in iodine metabolism leading to the synthesis of thyroid hormones were worked out, it was apparent that the failure of any one of these steps was genetically possible. Careful investigation with this in mind[28] has revealed at least three types of the disease, and more may be expected to occur. In one of the described types, iodotyrosines cannot be produced from tyrosyl residues and iodide, apparently because of a dysfunction of an oxidative enzyme. In another type, iodotyrosines cannot be coupled into iodothyronines with sufficient speed. In the third type, a dysfunction of the enzyme dehalogenase results in a failure of iodotyrosines of deiodinate.

Similarly, at least four genetic dysfunctions are now known among the six enzymes necessary for the interconversion of glucose and glycogen, and these result in four distinct forms of glycogen disease.[11]

Other examples could be cited. It has in fact become very important to search for genetic heterogeneity in all disease by appropriate methods.[29] Therapeutic measures which may be of value in one genetic form of a disease are not necessarily successful in another, even though the overt symptoms of the two may sometimes be quite indistinguishable.

Studies of clinical features, age of onset, genetic mode of transmission, immunologic and biochemical patterns, and other techniques may aid in discovering genetic heterogeneity. The use of a paper chromatography and electrophoresis has become of paramount importance in studies of this nature. Most recently, the development of techniques for separating individual human cells and growing them as pure clones in tissue culture has opened up new possibilities along these lines, as well as in the important area of the analysis of mutation rates.[30]

Structural Anomalies

It has long been my contention[31] that structural anomalies are just as subject to interpretation on the basis of enzyme dysfunctions as are the storage diseases and other obvious metabolic disorders. It should be possible by appropriate biochemical methods to discover errors of metabolism in the development of such conditions as lobster claw, polydactyly, achondroplastic dwarfism, and multiple exostoses, even though, apart from the morphologic aberrations, the subjects appear to be in good health. This conviction is shared by others,[8,32] and it is now possible to document it in some instances.

The first clear indication that a simple, gene-controlled enzyme dysfunction can be the basis for a structural anomaly came when evidence was found for a defect in glycolysis in the red cells in hereditary spherocytosis.[15,33] In this disease the red blood cells develop as spherocytes, lacking the expandable biconcave surfaces of the normal red cells. As a result, the cells are osmotically and mechanically fragile, and rupture easily as they move sluggishly into the spleen and are held there.

In the presence of the appropriate gene, one of the enzymes responsible for glycolytic metabolism fails to function properly. Since the gene involved is dominant, the basic defect in spherocytosis may well be the result of an inhibition rather than an absence of the enzyme. The enzyme affected appears most likely to be enolase, which in normal glycolysis converts 2-phosphoglyceric acid to 2-phosphoenolpyruvic acid. The latter substance in its subsequent metabolism provides energy in the form of adenosine triphosphate (ATP).

When enolase dysfunction occurs as a result of the activity of the implicated gene, the red cell can no longer build up adenosine triphosphate and maintain its usual store of chemical energy—energy necessary, among other things, for the maintenance of the integrity of the framework and the membrane of the cell.

Since the mature red cell appears to be the only cell of the body entirely dependent on glycolysis,[15] the defect would be most noticeable in this kind of cell, although the mutant gene must, of course, be present in all the cells of the body. Moreover, the red blood cell, being readily accessible for study, is of paramount importance as a tool for the analysis of many metabolic errors, even though the clinical effect is most noticeable in other tissues. For example, phosphogalactose-uridyl-transferase was implicated as the enzyme deficient or nonfunctioning in galactosemia by studies of the red blood cells of children suffering from the disease, and this was only later confirmed in regard to the cells of the liver, where most of the damage is actually done.[34-36]

Metabolic Interrelationships

Incidentally, biochemistry makes strange bedfellows of genetic diseases. Hereditary spherocytosis is now seen to be intimately related biochemically to galactosemia and the glycogen diseases through glycolytic metabolism, just as albinism, phenylketonuria, tyrosinosis, and alcaptonuria are all, surprisingly, biochemically related to one another through the metabolism of phenylalanine, one of the amino acids. In spite of the close biochemical relationships, however, the inheritance of such related disorders is quite independent and specific.

Since, of course, the metabolism of carbohydrates, fats, and proteins is closely integrated through the tricarboxylic acid cycle, it is well within the range of possibility that before too long the entire metabolic processes of man may be diagrammed as a single, elaborate biochemical pattern. Through the continuing study of more and more mutant individuals, each enzyme in the pattern will become identifiable in terms of the activity of a specific gene (a specific portion of a deoxyribonucleic acid molecule), and each genetic enzyme dysfunction will be related either to a mutation of that gene, resulting in a lack or modification of the enzyme, or to a mutation of a different gene, acting in such a way as to inhibit the activity of the enzyme.

The specification of the precise sequence of the steps in any reaction and the identification of precursors are enormously facilitated by the availability of mutants which block the various steps, since in the absence of such blocks the intermediary products are generally converted in the cell as rapidly as they are formed, and are thus difficult to detect. For example, the conjecture that phosphorylethanolamine is one of the long-sought, naturally occurring substrates of alkaline phosphatase was made possible by the availability of genetic instances of hypophosphatasia.[37]

Woven into the over-all pattern there will be, of course, environmental threads in the form of vitamins and other coenzymes, and of such things as hydrogen ion concentration, inorganic ion strength, temperature, substrate concentration, drugs, and infections.

Moreover, such a biochemical pattern of genetic health and disease will not be restricted to "physical" traits. Already several "mental" anomalies have yielded to biochemical analyses. Phenylketonuria and infantile amaurosis, among others, occur as the result of single-gene enzyme dysfunctions, as already mentioned. Other mental disorders are at present being actively investigated from this standpoint.

It should perhaps be pointed out here that the metabolism of metallic elements is also involved in human disease and may be genetically interfered with. Examples are the disturbances of iron metabolism in hemochromatosis and in methemoglobinuria, of copper metabolism in hepatolenticular degeneration, and of potassium metabolism in family periodic paralysis.[11,38]

The delineation of the complete genetic and biochemical pattern of man that I have envisaged involves, of course, many difficulties; but it also offers many challenges and promises important rewards. To give just one example, it would be of the utmost value in the elucidation of the basic mechanisms underlying heart disease to be able to formulate the metabolic interrelationships that must exist between the lipids and the purines. The relative levels of uric acid, cholesterol, and phospholipids have been shown to be related to the development of atherosclerosis and coronary artery disease.[39] Although the metabolism of each of these substances may be independently controlled by the activities of known genes, as in gout, xanthomatosis, and the lipidoses, respectively, some basic, underlying, genetic mechanism must surely exist which enzymatically conditions their interacting biochemical activities. A step in this direction may have been taken with the recent demonstration that familial amyloidosis represents an inherited aberrancy in lipoprotein metabolism.[40]

The most promising basis for the ultimate formulation of a complete chemical-genetic pattern for human beings lies in the now apparent principle of the unity of biochemistry—a principle which states that the fundamental biochemical reactions are identical for all organisms thus far studied, from microbes to man.

Practical Applications

The growing awareness that the primary activity of a gene is the control of the specificity of a substance such as an enzyme is adding immeasurably to the precision of the various practical applications of medical genetics. I have discussed these applications (diagnosis, treatment, prevention, and genetic prognosis) elsewhere in detail[41,42] and will add here only some suggestions regarding the emerging values of the principles discussed in this presentation.

It is clear that an understanding of the basic mechanisms of pathology is necessary for accurate differential diagnosis. In particular, the knowledge of the *basic genic action* involved will facilitate diagnosis, which is all too difficult in many diseases and aberrations at the present time. In those instances in which the biochemical steps between the primary activity of the gene and the resulting manifestation of the trait are few, the trait is likely to be readily diagnosable, and the primary activity may be subject to comparatively easy identification. But where the biochemical steps are numerous, with alternative pathways available, and with many opportunities for the impact of subtle or overt environmental influences, the resulting clinical picture may be complex and confused, and the basic genic action may be difficult to specify.

Another difficulty in the delineation of specific genic actions is to be found in those instances in which the effect of an individual gene is very slight. The effects which I have thus far discussed have been evident as marked phenotypic discontinuities. There are, however, genic activities in which the phenotypic effect of an individual gene is not readily discernible, consisting of only a very slight alteration of structure or function.

Where several or many such genes affect the efficiency of the same enzyme or process, however, their cumulative effects may be quite appreciable. Groups of genes with small but similar cumulative effects are referred to as polygenes, and they appear to be of importance in the genetically determined portions of quantitative variation, both normal and pathologic. Special methods are necessary for the analysis of the genetic and biochemical activities of polygenes.[42]

Each individual has a unique assembly of genes and will have his own mode of reaction to disease, whether it be presented through infection, trauma, stress, or mal-

nutrition, or wholly from within through biochemical error. The conviction that the genetic constitution is involved to a greater or lesser extent in all disease will serve as a stimulant to look beyond the secondary aspects of pathology and to search for the primary genic action in each case. Once this has been determined, both diagnosis and treatment will be facilitated. In this connection care must be taken that in assaying correlations between biochemical observations and clinical manifestations, cause is not confused with effect.

It is well to recognize that there is at present one apparent limit to potential therapy in genetic diseases. Although inhibitors, whether genetically determined or not, may be subject to environmental control, and although coenzymes and substrates may be provided nutritionally and in other ways, the basic protein enzymes can be gotten into a cell only by building them there. The building process is determined by the presence of appropriate genes.

As a consequence there would appear to be a residue of diseases, resulting from mutant gene-controlled absences of requisite, potent enzymes and apoenzymes, for which there is at present no apparent "cure" in the usual sense. The ingenuity of biochemists and physiologists may in the future, however, make it possible to devise allevation even for these fundamental errors.

The increasing ability to identify carriers of mutant genes will add to the precision of practical applications in prevention and in genetic prognosis, by bringing to light precursory, preclinical and constitutional stigmata which can be employed in these applications. The elucidation of indices of predisposition, whatever their origin, can be of service in identifying those environmental factors which may act as precipitating causes of clinical manifestations. Such identification may well prove to be of primary value in the ultimate control of disease.[43]

The prospects for the eventual understanding of human health and well-being grow ever brighter, and to no one is more appreciation due for his fundamental contributions to this field than to Sir Archibald E. Garrod.

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University of Hawaii, Honolulu, Hawaii

A Community Approach to

the

"Senior Citizens" Problem

JOHN W. DeVORE, M.D.
OSMA Committee on
Health Care of the Aged

LEAD BY A GROUP of Oklahoma City physicians, a committee of over sixty community leaders recognized the difficult problems confronting the senior citizen segment of the population and planned a retirement village to answer the growing needs of the aged and retired. Senior Citizens, Incorporated, and its proposed "Model Village For Senior Citizens," illustrate a unique *community* approach to a *community* health problem—that is being carried out without the paternalistic direction of federal planners.

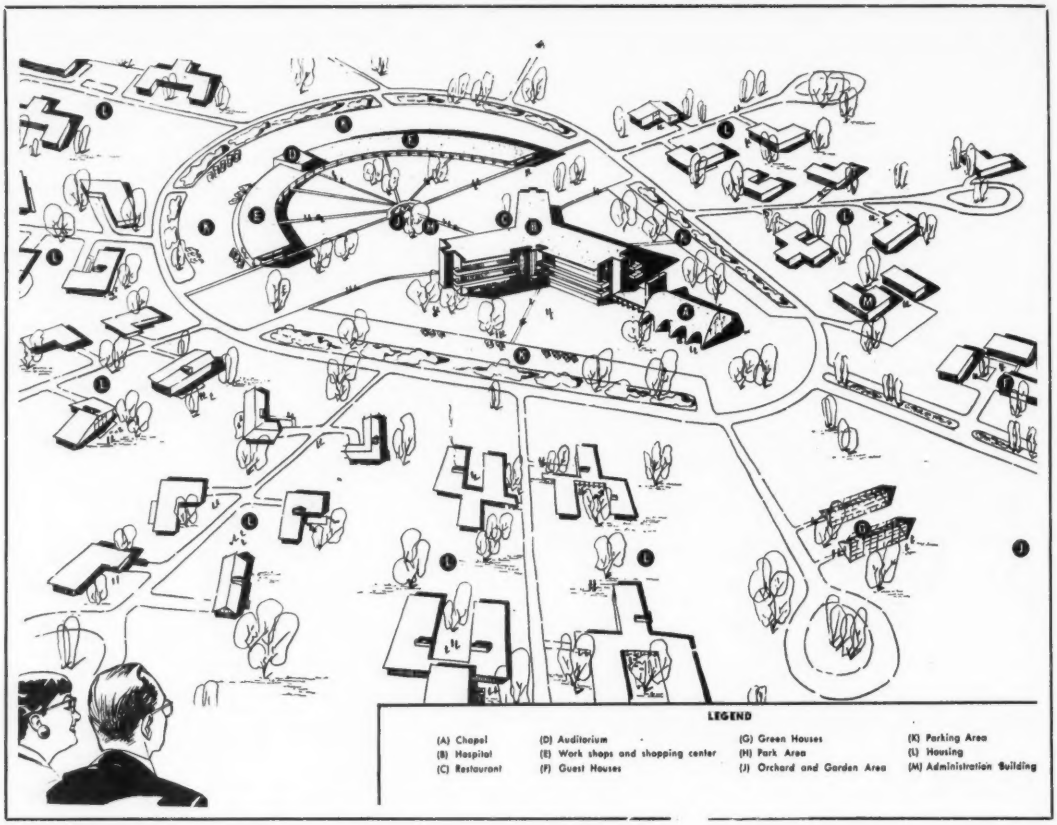
The Problem

Four years ago, a group of twelve, comprised of physicians, ministers, and community leaders, met to discuss the problem of aging which presented itself in Oklahoma City and in Oklahoma generally. It was recognized that Oklahoma City alone already had more than 30,000 people over sixty-five and that this figure would grow to 40,000 by 1970, according to estimates of population growth by the local Community Council. It was further recognized that, although there was a growing number of widows and widowers, couples have an average of twenty years longer life together today than they had fifty years ago. A decision was therefore made that any plans for the care of senior citizens should include adequate provisions for couples as well as for single individuals.

With these facts in mind, and with recognition of the many medical, economic, and social problems involved, the Council of Churches of Oklahoma City was asked to organize a planning committee to determine what should be done. Meanwhile, it was learned that the Altrusa Club, with Fannie Lou Leney, M.D., as chairman of their committee on aging, had been studying the problem for several years. The two groups combined efforts and worked with physicians and other church groups in the formation of the Senior Citizens Committee, the pilot group which later established Senior Citizens, Inc.

Since the Senior Citizens Committee was formed three years ago, the group has studied two hundred church and private homes for senior citizens and has investigated many rehabilitation hospitals and various church, city and state programs for care of the aged. From such research, the present plans have been formulated.

These plans call for the construction of a retirement village on a 320 acre tract at



MODEL VILLAGE FOR SENIOR CITIZENS

the edge of Oklahoma City. The village will represent a well-balanced community and will include the following: a rehabilitation and convalescent hospital; sheltered workshops; a shopping area; a recreation building as well as parks and other recreational facilities; guest houses for visitors; a green house and garden area; a chapel; and an administrative area to be built in a central location. Surrounding this area will be homes for individuals who are retired. The suggested master plan which is used as an illustration was drawn by Mr. John Turnbull of the Turnbull-Mills-Benham Architects and Engineers.

A plan of community action by local groups is the best answer to federal control. The maintenance of human dignity and self respect yields a greater sense of security to the individual than government assistance checks. Demonstration of the productiveness of the "aged" is the best rebuttal to mandatory retirement. Destructive social legislation is best defeated by providing a constructive solution to the problem rather than by a negativistic approach to the legislation. Senior Citizens, Inc., is a positive solution of a major social problem and is therefore worthy of the active and vigorous support of the medical profession.

Medical and Rehabilitation Facilities

A general hospital is not anticipated in the area, but rather a convalescent and rehabilitation facility. Various medical centers which have provided rehabilitation facilities have shown that over sixty per cent of the disabled elderly individuals, who in the past have been confined to their beds or to their rooms, can be rehabilitated to the point that they can at least care for themselves. Many return to gainful employment. Other individuals are made less dependent. A physician from one chronic disease hos-

pital reported that, prior to the initiation of rehabilitation, ninety per cent of the patients entering the hospital died there. With the new program, ninety per cent of those who enter are discharged able to care for themselves. In one home for the aged which was visited, there were fifty-eight occupants, all of whom had illnesses which would ordinarily place them in the completely disabled classification. Not one bed patient was present, primarily due to excellent physical therapy and occupational therapy.

The hospital is therefore being planned to care for short term minor illnesses, for convalescent care following hospitalization in a general hospital, and for rehabilitation of disabled individuals. The physical therapy, occupational therapy and recreational therapy provided to the hospitalized patients will also be available on an out patient basis to residents of the village and to individuals needing such care from surrounding communities.

One of the foremost fears of many elderly individuals is what would happen if an illness developed or an accident occurred in the home. When minor illnesses occur among individuals living in the village, visiting nurses will provide care in their own rooms or apartments when that is deemed advisable. In addition, there will be a call system for emergencies so that someone will be available night and day if an accident or sudden illness occurs in the individual's own quarters.

The direction of the care of each individual will be left entirely to the discretion of that individual's own private physician.

The hospital facilities are being planned by a committee having as chairman, Gregory E. Stanbro, M.D., with the following committee members: Wann Langston, M.D., Ella Mary George, M.D., Shelby Gamble, M.D., Fannie Lou Lenney, M.D., Arthur Elliott, M.D., James F. Hammarsten, M.D., Joseph McCain, Warren Young, J. J. Garver, the Reverend Tom Carter and the Reverend T. P. Haskins.

Occupational Facilities

Perhaps the greatest psychological hurdle which a retired individual has to cross is the idea that he is no longer a productive member of society. For some individuals, a hobby is adequate to meet their needs in this field, and their retirement income is adequate so that gainful employment is no longer necessary. The sheltered workshops will provide the facilities for such individuals.

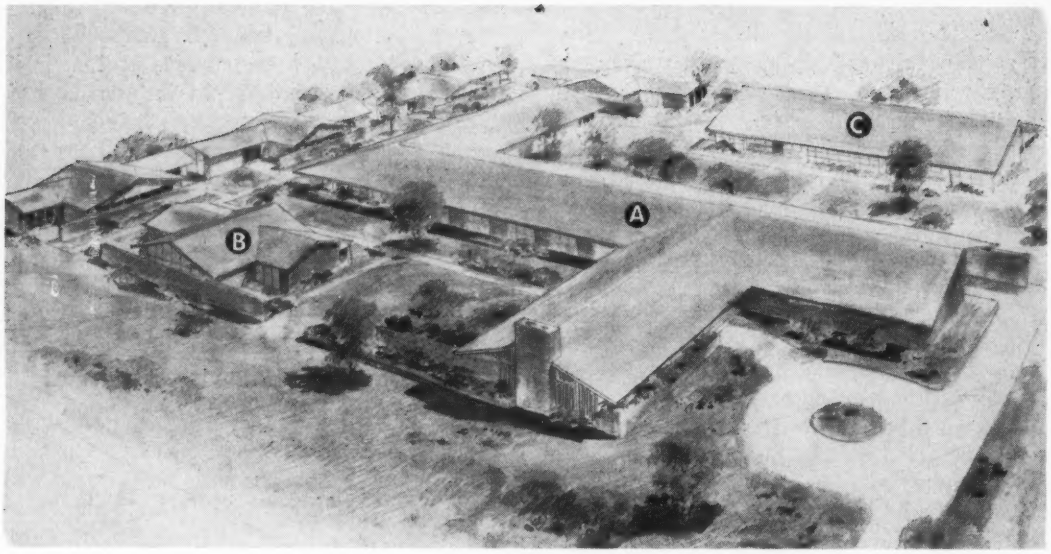
Other individuals have a great need for additional income or have the psychological approach that, unless their employment is gainful, they are no longer of use in the community or to themselves. There has been a growing need in the last few years for business and industry to find organizations who will accept contracts for piece-work and for special mailings and services. Through such contracts the sheltered workshops will supplement the income of the individual and permit him to work the number of hours and on the type of work which will meet his physical and mental capacity. Recent studies indicate that individuals in their seventies have an I.Q. equivalent to individuals in teenage group. To go with this they frequently have special skills and experience which make them invaluable in performing specialized work. For such individuals to enter forceful unproductiveness, is equally wrong for the individual and for society.

Recreation

An auditorium for lectures, concerts and major social functions is planned for the center of the sheltered workshop and shopping area. In addition, numerous types of both outdoor and indoor recreational facilities are being planned for use by residents of the village and their visitors.

Shopping Facilities

The village will be so large that, of necessity, any existing shopping area would be some distance away from the homes. Shopping facilities are being planned for the central area so that the basic needs of the residents can be met. A drugstore, clothing store, gift shop, grocery store and other shops to meet the basic needs of the residents are included. The shopping area will not be elaborate, so that, except for basic needs, the residents of the village would utilize shopping areas elsewhere in the city.



TYPICAL LIVING AREA

(A) Community House
(B) Duplex Apartment House
(C) Efficiency Apartment House

Restaurant

Attached to the hospital will be a restaurant or cafeteria for hospital personnel and ambulatory patients. It will be built in such a manner that residents of apartments and cottages who wish to have occasional or frequent meals away from their own home would be able to obtain such service within the immediate vicinity.

A committee has been formed to coordinate the development of occupational, recreational, shopping and restaurant facilities and to also work with the Hospital Facilities Committee in planning all aspects of an effective rehabilitation program. The members of this committee are: J. R. Stacy, M.D., Chairman; Hayden H. Donahue, M.D.,; Shelby Gamble, M.D.; Herbert Kent, M.D.; and Wendell Lillenas, M.D.

Housing

A goal has been set to provide housing for five hundred individuals within the next five years. The first 160 acre development is adequate space for an eventual two thousand individuals, with the second 160 acres being available for future expansion. A master plan for the entire area is being prepared to permit zoning and minimum standards of construction. As a general principal, housing will be a one-floor plan with construction embodying all possible safety features necessary for the prevention of home accidents and injuries.

Community housing units will provide private rooms with private baths for individuals, or small suites of rooms for an individual or couple. These community houses will have common dining facilities and multiple living rooms to permit various types of activity.

An informal park-like setting for all of the homes will also make possible limited access streets, preventing through traffic. A typical living area is shown in the suggested sketches by Mr. Tom Sorey of Sorey, Hill and Sorey. A housing unit, such as that illustrated, would accommodate thirty to

fifty individuals.

Most of the housing is to be built by church and civic organizations who wish to provide for their own members who are retired. The admission to such residences would be controlled by the organization building the homes. Senior Citizens, Inc., would build homes in one area to be leased to interested organizations so that individuals from small denominational groups, or from groups which do not have a housing area, would not be excluded. A multi-floored apartment building has been suggested to be built in this area. The committee handling this aspect of the work is comprised of: Earl Nichols, Chairman, E. W. Lippert, W. J. Mitchell, Tom Sorey, W. D. "Bill" Morris, Truett Coston, Warren Young, J. Gilbert Barker, John Turnbull, Joseph McCain, Jack R. Mills and Fannie Lou Leney, M.D.

Senior Citizens, Incorporated: Legal and Financial Structure

To facilitate the development of this retirement village, a foundation has been chartered as a non-profit corporation of Oklahoma under the name Senior Citizens, Inc. Attorneys for Senior Citizens, Inc. are now negotiating for the purchase of a specific tract of land on the Northwest Highway, situated on the edge of Oklahoma City. Mr. Ben Head and Mr. Duke Duvall have contributed innumerable hours in the formulation of the articles of incorporation and the by-laws of Senior Citizens, Inc. They have also assisted with the multitudinous legal questions which have arisen in the early formative days of the foundation.

The financing of the village will be, in large part, through self-liquidating, long-term loans. An effort is being made to raise the basic funds needed for purchase and initial development of the land as well as to obtain money from individuals who have a primary interest in the development of such facilities. Anticipated cooperation should make a public fund drive unnecessary. Many sources of funds are available when a project for retired individuals is once under way.

It has been the basic premise of the committee that facilities already present in Oklahoma City should not be duplicated and that the village should supplement the services to senior citizens living in Oklahoma City and surrounding communities. To plan the raising of funds, and to coordinate the facilities of the village with other facilities for senior citizens in Oklahoma City, a coordinating committee, under the chairmanship of Mr. John C. Wegner, has as its members the following: Mr. Bob Bryan, Mrs. George Townsend, Mrs. Douglas Yeager and Fannie Lou Leney, M.D.

Religious Activities

It has been recognized that the need for a deep religious faith is present in all people of all ages, but that the need is even greater in this age group. The village will have at its center an inter-denominational chapel. Every effort will be made to maintain the close contact of the individual resident with his own church after he moves into the village, but where that is not possible, he can attend religious services of his own faith in the chapel.

Summary

All of us recognize the growing needs of our country in the field of services to individuals who are retired. The plan herein presented is an attempt at a constructive solution to some of the problems involved. It is the feeling of the members of the subcommittees and of the many other individuals who have contributed their time to the Senior Citizens committee that the real solution to problems comes from local planning and administration. The maintenance of the dignity, self-respect and independence of the individual is of primary importance. Every possible facility to help each person look forward to a physically and mentally active and productive future is being incorporated in the plans which, in part, have been outlined in this article.

In the May issue, this series of articles sponsored by the O.S.M.A. committee will continue in the form of an analysis of nursing home problems of our state.

Medical News

First National Youth Conference on the Atom

A national Youth Conference on the Atom, the first such meeting of high school science students and teachers to discuss the peaceful uses of nuclear energy, will be held in Atlantic City, N. J., April 30-May 1.

Approximately 500 junior and senior high school science students and teachers will be sponsored in attendance at the conference by 60 or more electric utility companies throughout the country.

Organizations cooperating in the conference include the American Association for the Advancement of Science, Atomic Industrial Forum, Future Scientists of America Foundation, National Science Foundation, National Science Teachers Association, and Science Clubs of America.

The two-day conference is being held, sponsors said, to inform students and teachers about the many uses of the peacetime atom, and to help advance interest in the study of science. Among the speakers is Doctor John Laughlin, chief of the Division of Physics at Sloan-Kettering Institute for Cancer Research, who will speak on the uses of the atom in medicine.

The students and teachers attending the conference will tour the Atomic Energy Commission's new 1959 version of its major "Atoms for Peace" exhibit, which will visit Atlantic City during the week of the conference as the first stop in a nation-wide tour. In addition, the Atomic Energy Commission and more than 25 other organizations will have exhibits at the conference site.

Students who will attend the conference will be chosen in cooperation with local school authorities in a variety of ways, ranging from selection by school principals to essay contests and special examinations. They will be selected for their excellence and interest in science, particularly physics.

Public Apathy Threatens Polio Gains

Recent progress against paralytic polio is threatened by the fact that only half of the U.S. population under the age of 40 has had the full series of Salk inoculations, Health Information Foundation declared recently.

In its monthly statistical bulletin, *Progress in Health Services*, the Foundation pointed out that the number of cases of paralytic polio rose in 1958 after declining each year since the introduction of the Salk vaccine in 1955.

"Public apathy about the injections may be an unfortunate result of scientific progress," said George Bugbee, Foundation president. "Recent advances against polio have been so striking that many people may look upon it as a disease of the past."

Up to a few years ago, the Foundation reported, "polio was a wide-spread and constantly increasing danger, and little could be done to control it." The number of cases in this country rose steadily through the first half of the century, reaching a peak of almost 58,000 in 1952.

With the coming of the Salk vaccine, however, the incidence dropped sharply, and in 1957 only 5,500 cases (including 2,500 paralytic) were reported. "The evidence is now overwhelming," said the Foundation report "that the full series of three or more Salk inoculations provides a high level of protection from paralytic polio."

"Provisional figures for 1958 indicate that the number of cases rose to more than 6,000, including 3,100 paralytic cases. Most of last year's victims were persons who had not been fully vaccinated, and local epidemics were concentrated among the less advanced socio-economic groups, where levels of vaccination were lowest.

"The major problem today is to bring the benefits of the Salk vaccine to the entire

population, especially those under age 40," the Foundation stated. Estimates by the National Foundation for the end of 1958 indicates that 41 million persons in this age group had not been vaccinated at all, and an additional 16 million were incompletely vaccinated.

"Only 57 million—one-half of the population of this age group—had had the full series of three or more shots. Vaccinations were distressingly few during 1958. The need is sharpest at the preschool age and at 20-39, where only 45 and 30 per cent, respectively, are fully vaccinated."

Medical authorities suggest that the Salk vaccine protects against polio for at least three years and possibly longer, the Foundation reported. Moreover, "no break in the safety of the vaccine has shown up since 1955."

Current research efforts cited by the Foundation include an attempt to develop a more powerful vaccine that can be taken by mouth. But "universal immunization" with even the present vaccine could signal "the virtual end of mankind's most destructive diseases."

Ob-Gyn Schedules Examinations

The American Board of Obstetrics and Gynecology have scheduled examinations (Part II), oral and clinical for all candidates for May 8 through 19, 1959 at the Edgewater Beach Hotel, Chicago, Illinois. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participate in the Part I Examination will be notified of their eligibility for the Part II Examinations as soon as possible.

The deadline date for the receipt of new and reopened applications for the 1960 examinations is August 1, 1959. Candidates may submit their applications at any time before that date and are urged to do so by writing to Robert L. Faulkner, M.D., Secretary-Treasurer, 2105 Adelbert Road, Cleveland 6, Ohio.

Oklahoma Pharmacy Dean Honored by Drug Company

An oil painting of Dean Clark was presented to the College by Wyeth Laboratories, during the Annual Pharmacy Seminar held at the Lockett Hotel, Norman. The presentation was made by H. A. Dicken, Wyeth district sales manager. Roy F. Spreter, noted artist, executed the portrait.

In his remarks, Mr. Dicken cited Doctor Clark's 38 years of widespread experience in almost every phase of pharmacy, and depicted the Dean as " . . . a distinguished member of the teaching profession, and a common rallying point for every branch of pharmacy."

Mr. Dicken related to the audience many of Dean Clark's accomplishments, including his service as editor of both the *Wisconsin Druggist* and the *North Carolina Journal of Pharmacy* and his authorship of "Orientation In Pharmacy," a book designed to guide pharmacy students in their selection of a position after graduation.

He cited Doctor Clark's adaptation of the College of Pharmacy to the community's needs, his pioneer role in the introduction of hospital and veterinary pharmacy courses to the College's curriculum, and his experience in retail pharmacy and drug manufacturing.

Ethics and Exigencies

Does the Industrial Physician have any obligation to care for non-industrial medical problems? What yardstick may one use to delineate the frequently disputed boundaries between industrial and private practice? Granted that there will never be complete agreement as to just where one takes up and the other leaves off, a few fundamental concepts will help in the majority of cases. The most important guidepost on this, at times, difficult road of decision is recognition of the fact that the structure of medical ethics is based primarily on welfare of the patient. The second is appreciation of the fact that the industrial physician complements and does not attempt to supplement or compete with the family doctor. There are a number of areas that are certainly not "industrial", yet properly require a measure of attention from the industrial physician, the degree of such attention being determined on the merits of each case. To illustrate; few would question the obligation of the industrial medical department to furnish immediate care to the employee brought in with a "coronary". When available, oxygen, analgesics and whatever else is needed should be administered and the employee cared for until safe transition can be made to the hospital and the care of his personal physician. How far should the industrial physician go in *diagnosing* a complaint that is not felt to be of industrial origin? If the presenting complaint is one that *might* portend an immediately serious condition which could be confirmed or ruled out by a few simple procedures, then those may well fall into the province of the industrial physician. Here chest pain or abdominal pain of doubtful origin are good examples. A few searching questions, examination and selected lab work may be done expeditiously and if findings warrant, referral made to private physician for further study and/or treatment. Most important, smooth transition to the personal M.D. is made when the industrial physician discusses the findings with him. Unless this is done in such cases, the employee may often, to his detriment, fail to pursue the matter further.

Finally, the industrial physician has an obligation in the field of preventive medicine. The minor non-industrial conditions for which he is consulted are legion. Frequently a word of advise or simple first aid averts more serious trouble with absenteeism and its economic penalties. In other cases the need for referral to the family doctor is readily recognized and effected to the benefit of all concerned.

Prepared by OSMA Committee on Occupational Medicine

First Conference on Handicapped Children Held

The First Annual Conference on Handicapped Children was held March 13 and 14 in Oklahoma City.

The purpose of the conference was to bring into one meeting all governmental, religious, non-profit, and private agencies or organizations that are interested in the problems of handicapped children, with the hope that there could be a greater correlation of the efforts of all parties in developing higher standards of care for this group. The conference adopted by-laws and elected an eighteen member board of directors.

Guest speakers were George H. Schade, M.D., Director of Mental Health Unit, Department of Pediatrics, University of California Medical Center, San Francisco; A. R. Shands, Jr., M.D., Medical Director, Alfred I. duPont Institute of Nemours Foundation, Wilmington, Delaware; Eric Denhoff, M.D., Medical Director, Meeting Street School for Handicapped Children, Providence, Rhode Island; and Romaine P. Mackie, Ph.D., Chief, Exceptional Children and Youth Division, Office of Education, Department of Health, Education and Welfare, Washington, D.C.

The conference was under the sponsorship of the Oklahoma Chapter of the American Academy of Pediatrics, the Oklahoma Orthopedic Society and the Nemours Foundation of Wilmington, Delaware and was coordinated by the Oklahoma City Junior League. Over 600 person from all sections of Oklahoma attended the conference.

THE CITATION

MEDICO-LEGAL BRIEFS

Prepared by the Law Department of the American Medical Association

COMMISSION ON MEDICAL CARE PLANS AND LAWS RELATING TO SUCH PLANS—The Commission on Medical Care Plans which was appointed by the Board of Trustees in 1954, submitted its report to the House of Delegates at the Clinical Meeting in December 1958. The House decided to defer action on the report until the Annual Meeting in June 1959. At the same time the House requested the constituent associations to arrive at some decisions in regard to the following two questions and submit them to the AMA's Executive Vice President sixty days in advance of the June 1959, Annual Meeting:

"1. *Free Choice of Physician*—Acknowledging the importance of the free choice of physician, is this concept to be considered a fundamental principle, incontrovertible, unalterable, and essential to good medical care without qualification?

"2. *Closed Panel Systems*—What is or will be your attitude regarding physician participation in those systems of medical care which restrict free choice of physician?"

MEDICOLEGAL MEETINGS — In the last issue of "The Citation" the dates for the regional medicolegal meetings to be sponsored by the AMA were incorrectly listed. The meetings will be held on March 20-21 in Washington, D.C.; April 3-4 in Cleveland, Ohio; and on April 17-18 in Salt Lake City.

The programs for the meetings have not been completed as yet; however, some of the subjects that will be discussed are: Medical and Legal Problems Involved in Narcotic Addiction; Traumatic Neurosis; the Approach of Medicine and the Law to Contingent Fees; Res Ipsa Loquitur in Professional Liability Cases; Impartial Medical Testimony; and the Classic Method of Cross Examining an Expert Medical Witness.

Several outstanding speakers have already agreed to participate. Included are Rufus King, Washington, D.C.; R. Crawford Morris, Cleveland, Ohio; Truman Rucker, Tulsa, Oklahoma; Father Robert F. Drinan, Dean, Boston College Law School; Irving Goldstein, Chicago, Illinois; and Doctor Robert H. Felix, Bethesda, Maryland.

At each of the meetings the sessions will be presented for half a day on Friday and a full day on Saturday. Luncheon will be served on Saturday, with no planned program for Friday night. The registration fee for each conference will be $5.00, to cover the cost of the luncheon and a copy of the proceedings. Advance registrations should be mailed to the Law Division, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

MEDICAL PROFESSIONAL LIABILITY—This was a medical professional liability suit against a physician for the death of a patient from bronchial pneumonia with chicken pox as the antecedent cause. During one of his visits to the patient, the physician stated that "This is a hospital case but they won't take her on account of this other" (the chicken pox). After her death, the physician stated: "I should have put her in the hospital." The California District Court of Appeals held that: "The two statements taken together clearly make a case sufficient to give to the jury" and accordingly reversed the judgment of a non-suit.

Sheffield v. *Runner*, 328 P. 2d 828 (Calif., Aug. 19, 1958).

Further information on the preceding cases may be obtained from the Law Department, American Medical Association, 535 North Dearborn Street, Chicago, Illinois.

Coming Meetings

UNIVERSITY OF OKLAHOMA MEDICAL CENTER

POSTGRADUATE PROGRAM

Oklahoma City, Oklahoma

Individual Postgraduate Courses

FIFTH ANNUAL COMBINED SURGERY, RADIOLOGY, PATHOLOGY SYMPOSIUM—May 8 and 9

Diagnosis and Treatment of Thyroid Diseases.

Sponsored by the Oklahoma Association of Pathologists, Oklahoma Association of Radiologists and Oklahoma Chapter of American College of Surgeons. Guest participants of national reputation in surgery, radiology and pathology will participate.

OKLAHOMA ASSOCIATION OF HOUSE STAFF PHYSICIANS—May 22

Two guest lecturers and presentation of original papers by members of the various house staffs will highlight this program. Participating hospitals are: Hillcrest Medical Center, Tulsa, St. John's, Tulsa; McBride, Mercy, St. Anthony, University, Veterans Administration, Wesley, Oklahoma City; Central State Hospital, Norman.

SERIAL POSTGRADUATE COURSE

Postgraduate Division

UNIVERSITY OF OKLAHOMA MEDICAL CENTER

Oklahoma City, Oklahoma

1958-1959

May 13 — Pediatrics — Antimicrobial Therapy and Treatment of Infectious Disease in Childhood.

June 10—Surgery—Herniae.

Designed so physicians may attend four hours of formal instruction in the above fields while spending only one-half day from their office, this series is approved for credit by the Oklahoma Academy of General Practice. Time will be 3:30 to 8:30 p.m. on the Second Wednesday of each month, September through June. Registration is $3.00 per session or $25.00 for the entire series.

Further information concerning the individual and serial courses may be obtained from the Office of Postgraduate Education, University of Oklahoma School of Medicine, 801 N. E. 13th Street, Oklahoma City, Oklahoma.

AMERICAN GOITER ASSOCIATION

April 30, May 1, and 2 **Drake Hotel**

Chicago, Illinois

The program for the 1959 meeting of the American Goiter Association will consist of papers dealing with the thyroid gland, its physiology, pharmacology, pathology and therapy.

Further information is available by writing to John C. McClintock, M.D., Secretary, 149½ Washington Avenue, Albany 10, New York.

13th ANNUAL

ROCKY MOUNTAIN CANCER CONFERENCE

July 22-23, 1959 **Brown Palace Hotel**

Denver, Colorado

The Rocky Mountain Cancer Conference will be held at the air conditioned Brown Palace Hotel in Denver, July 22 and 23, 1959. Further information concerning the program and reservations may be obtained from Rocky Mountain Cancer Conference, 835 Republic Building, Denver 2, Colorado.

53rd Annual Meeting

of the

Oklahoma State Medical Association

April 20, 21, 22, 1959 **Mayo Hotel**

Tulsa, Oklahoma

Organization News

Service Contract for Old Folks To Highlight Annual Meeting

Highlighting policy decisions to be made at the Annual Meeting of the House of Delegates on April 19, will be a joint report from OSMA's Blue Shield Liaison Committee and the Health Care of the Aged's subcommittee on Insurance and Retirement. President Mohler has asked these groups to evaluate the AMA's request for the development of a service-type pre-payment program for the over-65-age-group.

The Big Picture

At the AMA Interim meeting in Minneapolis, the House of Delegates adopted a report urging the development of special insurance and pre-payment programs for senior citizens with "modest resources and low family income." The report urged the profession to "continue to assert its leadership and responsibility for assuring adequate medical care for this group of our citizens."

More specifically, the report asked all constituent and component medical societies to " . . . expedite the development of an effective voluntary health insurance or prepayment program for the group over 65 with modest resources or low family income; that physicians agree to accept a level of compensation for medical services rendered to this group, which will permit the development of such insurance and prepayment plans at a reduced premium rate."

In response to this report, the National Association of Blue Shield Plans issued a policy letter supporting the practicability of establishing an in-hospital program, with full-service fees to be offered below certain income ceilings as established in conformity with the economic level of the area to be served.

The AMA Committee agreed with the Blue Shield proposal, with the exception that it feels a major effort must be made to provide an alternative to hospitalization. It was agreed by the Committee that every effort should be made to provide for a specified number of office and home calls per year and that a provision for payment of calls to nursing homes should be included as an alternative to hospitalization.

As evidenced by the recent introduction of several commercial insurance programs for senior citizens, private industry and the medical profession are attempting to take immediate action designed to thwart the threat of the proposed Forand Bill. This bill, now before the House Ways and Means Committee, will provide medical, hospital, dental and nursing home care, through the Social Security system, for about fourteen million persons.

Some medical leaders, however, are looking beyond the immediate danger of the Forand Bill and foresee increasing problems regarding the health care of the aged in the years to come. It is apparently generally agreed that private industry must make some provision to take care of this growing segment of the population, or the government will surely pass some type of provisional legislation.

To illustrate the concern being expressed in Washington circles, the President has ruled that the Federal Council on Aging should be expanded, given full cabinet status, ordered to make a prompt study of the needs of the aged and determine how government can help meet them. Both major national parties have also zeroed in on aging problems as a powerful political issue. For example, the Republican National Committee, stimulated by statistics indicating that one out of every four voters will be more than 60 years old in 1960, is making a strong effort to establish Senior Republican Clubs throughout the country.

Several state medical societies have already taken some action toward the solution of the aging problem within their states and it is anticipated that the AMA request for action will hold the limelight at every state association annual meeting in the country.

Oklahoma's Position

Traditionally, most Oklahoma physicians have long opposed a service-type contract for medical services and have vociferously supported the philosophy behind the prevailing indemnity Blue Shield program, where physicians have the option of assigning additional fees beyond the prescribed Blue Shield payment.

Many feel that any approval of a service plan by the House of Delegates will represent a major departure from existing policies. Proponents of the service program for low-income senior citizens point out, however, that the adoption of such a program is simply a realistic approach to a heretofore unsolved problem, involving less than ten per cent of the state's population, and does not necessarily represent a compromise of principle.

Doctor Mohler's study group is thus involved in the evaluation of an extremely controversial subject. On March 18, Hayden H. Donahue, M.D., Chairman of the Committee on Health Care of the Aged, Earl D. McBride, M.D., Chairman of the Sub-Committee on Insurance and Retirement and Henry T. Russell, M.D., Chairman of the Blue Shield Liaison Committee, met with representatives of Blue Cross-Blue Shield for a preliminary discussion of the possibilities and propriety of developing a program for Oklahoma.

Following this meeting, the committees of Doctors Russell and McBride met for four hours on Sunday, March 22, for further consideration of the proposal. After hearing various plans that may be possible to initiate in Oklahoma, the group voted to establish a smaller committee, under the leadership of Doctor Donahue, to carry out an immediate and comprehensive analysis of the alternate plans that are apparently available. The special committee will assemble on April 4, at which time definite recommendations will be formulated for presentation to the large group on the following day.

The final report on this subject will be presented to the Council on April 18 and then be passed on to the House of Delegates on the following day, with or without a recommendation from the Council.

Other Controversial Issues

As mandated by a resolution passed at the 1958 annual meeting, all county medical societies have been informed of known controversial issues to be brought before the House of Delegates at the 1959 meeting in Tulsa.

In addition to the health insurance proposal, it is anticipated that the Delegates will be asked to pass judgment on the following questions:

1. Whether to clamp down on hospitals that are allegedly collecting physician's fees for the care of Welfare recipients. A special study committee is now investigating this situation and its findings have not been finalized at this time.

2. Ratification of the DPW committee's recommendation pertaining to the handling of welfare medical claims, to wit:
   "Each claim completed by a physician will state whether the claimant is under salaried contract, or on retainer by the hospital where the patient received his treatment. If under contract, or salaried, or on retainer, the claim will be disallowed."

3. In the event Senate Bill 20 becomes law (pertaining to the transfer of the functions of the Crippled Children's Commission to the Department of Public Welfare), the House may be asked to change the present policy of performing complimentary service for ADC cases which are now processed through the machinery of the CCC.

4. Delegates may be asked to ratify the implementation of a previously endorsed, optional method of receiving compensation for the medical care of welfare recipients. Under this plan, physicians would have the option of consigning their payment for services directly to another agency, institution, trust fund, etc. County societies are being polled regarding this proposal by the DPW committee.

5. Action must be taken on a resolution calling for a constitutional amendment to make AMA dues optional rather than mandatory.

OSMA, Others Favor Radiation Bill

House bill 583, an act relating to atomic energy, ionizing radiation and radiation protection, is receiving active support from several groups as it is being processed through the channels of the 27th State Legislature.

The bill, introduced by Representative Goodfellow of Anadarko, includes the recommendations made by an advisory committee comprised of physicians, engineers, hygenists and representatives of the State Department of Health. Lucien M. Pascucci, M.D., Tulsa, and Kieffer Davis, M.D., Bartlesville, served on this committee. Physicians serving on the Public Policy Committee of the OSMA have also reviewed this piece of legislation and endorsed its principle.

If passed, the bill will establish regulatory procedures for governing the safe use of radioactive materials or devices capable of producing ionizing radiation. The purpose of such a law is to encourage the beneficial uses of ionizing radiation in manufacturing, agriculture, research and other gainful purposes and to prevent and control any harmful effects arising from misuse of such radiation.

The proposed model law recognizes the use of radiation as a potential health problem and places the administration of the act in the State Department of Health. One of the important features of the proposed law provides for the establishment of a Radiation Advisory Committee composed of twelve qualified members who are to advise the Commissioner of Health on needed rules, regulations and standards of radiation protection. Members of this committee will receive no compensation.

The Atomic Energy Commission has endorsed the adoption of radiation protection laws by the various state governments to insure the safe use of radioactive materials sold by the Commission to private users. To date, eight states have adopted such acts placing the administration in the respective health departments.

At the present time, the bill is in the Appropriations and Budget Committee of the House of Representatives.

O.U. Students to Attend Student AMA Meeting

Six medical students from the Oklahoma University Chapter of the Student American Medical Association will represent their state at the organization's annual convention in Chicago, April 30 through May 3. At this time, only three of the Oklahoma delegation have been named by Herschel L. Douglas, President of the local chapter. In addition to himself, Ed Brandt, Chairman of the National Committee on Graduate Education, and William Kirkham, National Treasurer, are planning to attend.

Scientific papers and exhibits by more than a score of students, interns and residents and presentations by leaders in medicine, including Alton E. Ochsner, M.D., will highlight the ninth annual meeting, to be held at Chicago's Shearton Hotel.

Representing all parts of the nation, the program participants were selected from a record-breaking flood of applications.

In addition to the scientfic portion of the meeting, other events include: the Association's House of Delegates meeting, a concurrent meeting of the SAMA Woman's Auxiliary, annual banquet and dance, and a special party sponsored by the Abbott Laboratories where more than 2,000 guests will be entertained with dancing, refreshments and a Broadway floor show.

Vets Medical Care Leaflets Available

The AMA Committee on Federal Medical Services has released three leaflets on the profession's policies toward veterans' medical care. Entitled "How to Cut Your Medical Bill," "Gigantic Giveaway" and "What About the Veterans Family," the leaflets are available through the Council on Medical Service, AMA.

Six Oklahoma M.D.'s Slated To Undertake National Legislative Program

Six Oklahoma physicians, one from each of the congressional districts are being asked to build national legislative teams within their respective districts. The appointments represent an effort on the part of the Public Policy Committee and John E. McDonald, M.D., Tulsa, member of the AMA Legislative Committee, to re-vitalize Oklahoma's activities in the promotion of the AMA's legislative program on a local basis.

The physicians accepting the district assignments will serve as a National Legislative Sub-Committee to the Public Policy group, but, more importantly, they will hold key positions at the "grass roots" level of legislative communication. Under the new system of communication, information and materials on national bills affecting health care will come to the OSMA through the AMA's Washington Office and Legislative Committee. Suggested action will be evaluated at the state level and a definite program will be developed by the Public Policy Committee and the Sub-Committee. The Sub-Committee members will then carry the plan back to the organizations within their congressional districts and build effective information campaigns as deemed necessary.

It is felt that membership in the district organizations may well be opened up to other professional groups, civic leaders, and any others who are interested in good government and willing to do something about it. However, the composition of the district "teams" will be left entirely to the discretion of the physician in charge, who will have complete authority and responsibility for the success or failure of a national legislative program within his district.

The group will hold an indoctrination meeting during the annual meeting of the OSMA on Monday, April 20. At that time, basic goals will be outlined by Doctor Gunnar Gundersen, President of the American Medical Association and Mr. Glenn Gillette, member of the AMA's Field Service Division. J. R. Stacy, M.D., Chairman of the Public Policy Committee, and Doctor McDonald will then brief the group on a definite course of action to be taken on specific pieces of legislation that are considered to be of sufficient impact for a first priority assignment.

Serving as the most important link in the channel of communications, will be the following physicians: Worth M. Gross, M.D., Tulsa, District I; Tom S. Gafford, Jr., M.D., Muskogee, District II; J. Hoyle Carlock, M.D., Ardmore, District III; Clinton F. Gallaher, M.D., Shawnee, District IV; William N. Harsha, M.D., Oklahoma City, District V; and Paul B. Lingenfelter, M.D., Clinton, District VI.

OSMA Hosts AMA Committee

On April 11, Oklahoma City and the Oklahoma State Medical Association hosted a regional meeting sponsored by the American Medical Association's Committee on Maternal and Child Care. A group of physicians, representing ten states of this area, met to discuss maternal and perinatal studies that are being conducted throughout the country.

Perinatal, a relatively new term, involves the period of time during pregnancy and within thirty days following delivery. Medical men have recognized the need for further study of the mortality and morbidity cause and frequency within this area and the AMA Committee, working under the Council or Medical Service, is correlating the work being done by the states.

Oklahoma was one of the first states to undertake such studies. The studies are being sponsored jointly by the Oklahoma State Medical Association, the University of Oklahoma School of Medicine and the State Department of Health.

Following the regional meeting, held at the Skirvin Hotel, the AMA Committee met on April 12 at the OSMA executive offices.

The large structure, left, is Hillcrest's new Maybee Children's Center. At right is the new general wing.

Hillcrest Medical Center Opens Two New Wings

Tulsa's Hillcrest Medical Center recently opened two new wings which were erected at a cost of $4 million. This gives the center a total of 800 beds.

Mabee Children's Hospital

The six-floor Mabee Children's Hospital wing, built at a cost of $2 million, features the latest equipment as well as many innovations for hospital care of children. The facility is a gift from the J. E. and L. E. Mabee Foundation.

An x-ray therapy department is located in the wing basement. Equipment to be installed later includes a cobalt-60 machine.

The first floor houses the micro-chemical laboratory where tests will be made on the young patients. On the second floor, a diagnostic x-ray section has been installed.

Patients in the 3½ to 8-year old category will be treated on the fourth floor. Cribs and bassinets have been located on the fifth and sixth floors to care for 1-day to 3-year-old patients. Isolation wards are provided on the third floor as are facilities for the care of adolescents.

Each room has a play room, properly equipped for the age range. A combined kitchen and nurse's workroom also has been provided on each floor level. In these kitchens, "irregular" meals and special formulas will be prepared.

Each room may be converted into a private or semi-private unit, thus enabling parents to stay with their children. Glass has been used extensively in the internal walls to permit maximum observation.

General Bed Wing

The new north wing houses the main entrance, admission administrative offices on the ground floor. On the fourth floor, seven new operating rooms have been constructed. All have new lighting systems with explosion-proof electrical outlets.

All beds are electrically operated and have access to oxygen, vacuum and intercom systems.

Medicare Brass Alarmed About Delayed Billings

In a recent communication from the Office of Dependents' Medical Care, concern was expressed about Medicare claims which have been delayed for a considerable period of time after the care was rendered. Government officials point out that delayed billings not only work a hardship on the dependents, the fiscal contractors and the source of care, but also hamper the accurate preparation of budgetary requests and required statistical data.

Suggested Handling of Future Claims

The correspondence emphasized that Medicare contracts call for payment to be made on the basis of "complete" claims and urged hospitals and physicians to obtain all necessary information, including Medicare Permit if required, or make arrangements for obtaining same, at the time the patient makes the initial visit and at the time an understanding is reached that care will be rendered under the program.

It was pointed out that the eligibility of the patient should be substantiated from information contained or DD Form 1173 (Identification Card) or from other documentation establishing that the patient is an eligible dependent of an active duty member of the Uniformed Services. After eligibility has been determined and properly documented the medical service should be performed, followed by the prompt filing of a claim for compensation.

Old Claims May Be in Jeopardy

Although it was not stated specifically, it was implied by the government release that physicians holding old claims on their desk may encounter some future difficulty in collection. An urgent plea was expressed that physicians and hospitals "complete" and submit old claims as soon as practicable. The correspondence repeatedly spoke of the difficulty of processing such claims and resolving any difficulties associated with them after the passage of considerable time between the rendering of service and the billing.

A.M.A. Annual Meeting In Atlantic City

Approximately 15,000 physicians are expected in Atlantic City, New Jersey for the 108th Annual Meeting of the American Medical Association which will be held June 8-12th. Atlantic City will be hosting the five-day convention, the world's largest medical meeting, for the 16th time.

New medical research findings and methods of handling daily medical problems will be reported by 500 physicians in scientific papers or participation in symposium and discussion groups.

New Look for Atlantic City

Since 1955, when the A.M.A. last met there, Atlantic City boasts 4,000 new motel units and millions of dollars have been spent in remodeling and modernizing several of the larger hotels. According to A.M.A. Convention Officials, "the charm of this vacation spot has been retained while the comforts have been vastly improved."

Of particular interest to the visitors at this season of the year will be the excellent fishing afforded at Cape May, just 40 miles south of Atlantic City.

The proximity of New York City is an additional attraction for the visiting physicians and their wives, as it is only a two hour drive from the convention city.

Advance hotel and meeting registration information is available by writing to Convention Service Department, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

Record Enrollment Seen For Health and Accident Program

Enrollment in the Association's new health and accident insurance program has reached record proportions, according to figures recently released by the North American Accident Insurance Company, underwriters of the program.

From December 15, the beginning of the enrollment period, through April 1, 778 members of the O.S.M.A. have become insured under the master policy. This number includes new enrollees as well as physicians

who have transferred their coverage from the old North American program to the improved plan which replaces it. Since nearly two hundred physicians have not yet transferred from the old to the new, the total enrollment picture looks even brighter, with nearly a thousand participants being virtually assured. The previous program was carried by 760 physicians.

Enrollment Period Extended

The charter enrollment period originally scheduled to end on April 15, has been extended by the insurance company until May 15. The principle reason for the increased latitude is to allow more time for company representatives to make personal calls on physicians. Another reason for the extension is to allow prospective physicians an opportunity to visit the North American exhibit at the O.S.M.A. Annual Meeting April 20-22, Tulsa.

Extension of the charter enrollment period will enable more physicians to come into the program without evidence of insurability. Under the terms of the master contract, all members who transfer or submit new applications before the expiration of this period will be assured of at least $200 per month coverage, regardless of physical condition. Those insured under the old program will receive full return of unearned premium at the time of transfer, or they may wait until their next premium due date to change. Most physicians will be able to secure $600 per month coverage if they are under 60 years old and in reasonably good health.

Brochures have been sent to every physician in the state and sample master contracts are now being mailed to county medical societies. It is important to note that an individual certificate can be cancelled only for non-payment of premium, attainment of age 70, termination of O.S.M.A. membership or retirement from the active practice of medicine. Any other termination of coverage would have to result from the unlikely cancellation of the master contract by either the O.S.M.A. or the insurance company, with ninety days notice of such action being a mandatory feature of the master contract.

James P. Jobe, M.D., Honored

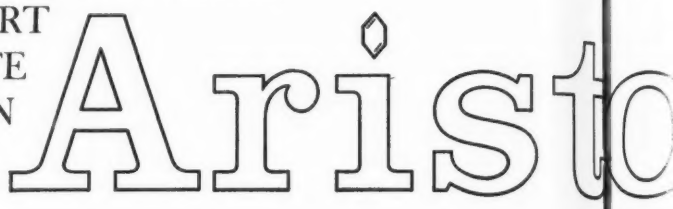
James P. Jobe, M.D., was recently honored when the El Reno Junior Chamber of Commerce awarded him their Distinguished Service Award. The honor was in recognition of his many professional, civic and religious activities in El Reno. The organization had previously elected him to the office of Vice-President.

From a professional standpoint, Doctor Jobe belongs to the Oklahoma State Medical Association, the American Medical Association, the Oklahoma A.A.G.P., the American Academy of General Practice, the Oklahoma State Heart Association and the American Heart Association. In addition, he is serving as President of the Canadian County Mental Health Association, Secretary of the Canadian County Medical Society, Medical Advisor of the Canadian County Heart Unit and as a member of the Professional Education Committee of the State Heart Association.

A deacon in the First Baptist Church and President of the Training Union also teaches and sings in the choir.

Additional activities of the physician include participation in the Lions Club, and sponsorship of the Pre Med Club, a group which offers vocational guidance for students entering medicine and allied fields.

NOW—YOU CAN GET THE UNSURPASSED ADVANTAGES OF ARISTOCORT IN SALICYLATE COMBINATION



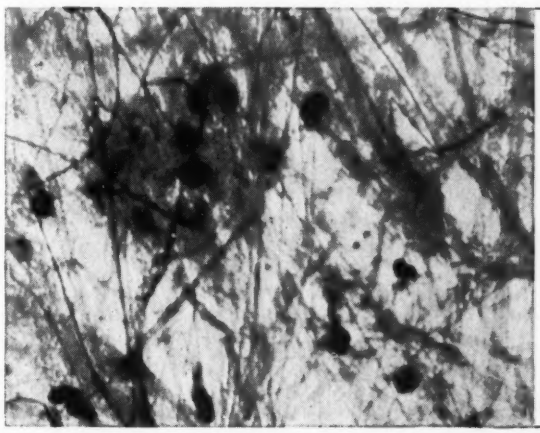
Aristogesic combines the *anti-inflammatory* effects of Aristocort® Triamcinolone with the *analgesic* action of a most potent salicylate. This means that the dosage of each is *substantially lower* than that ordinarily required for each agent alone. With Aristogesic the physician has exceptionally wide latitude in adjusting the dosage to the lowest effective level.

The possibility of gastric distress from either salicylamide or corticosteroid is minimized because of lower dosage required. This is further reduced by the buffer action of aluminum hydroxide. And the ascorbic acid helps meet the increased need for this vitamin in stress conditions. Because of the low dosage, side effects with Aristogesic have been relatively infrequent and minor in nature. However, more serious side effects have traditionally been observed on all corticosteroid therapy. Patients on long-term Aristogesic therapy should, therefore, be observed carefully.

Aristogesic*

Steroid—Analgesic Compound LEDERLE

for relief of *chronic*—but *less severe* pain of rheumatic origin



Indications: Mild cases of rheumatoid arthritis, tenosynovitis, synovitis, bursitis, mild spondylitis, myositis, fibrositis, neuritis and certain muscular strains.

Dosage: Average initial dosage: 2 capsules 3 or 4 times daily. Maintenance dosage to be adjusted according to response.

Each Aristogesic Capsule contains:

ARISTOCORT® Triamcinolone	0.5 mg.
Salicylamide	325 mg.
Aluminum Hydroxide	75 mg.
Ascorbic Acid	20 mg.

Supply: Bottles of 100.

Collagen tissue (x250)

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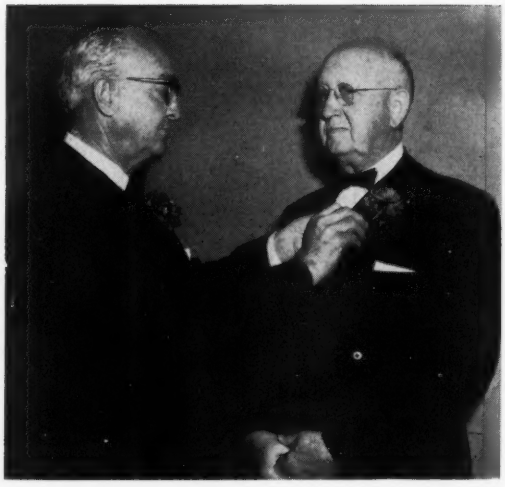

Pictured above, R. Q. Goodwin, M.D., 1955-56 President of the Oklahoma State Medical Association, is shown presenting 50 Year Pins to O. R. Gregg, M.D. (left photo) and Edward F. Stephens, M.D. (right photo).

Two Norman Physicians Honored At Doctor's Day Celebration

The Annual Doctor's Day celebration of the Cleveland-McClain County Medical Society Auxiliary provided an appropriate opportunity for auxiliary members and physicians alike to pay tribute to two Norman men of medicine. O. R. Gregg, M.D. and Edward F. Stephens, M.D. were extended appreciation for their combined 100 years of medical service when R. Q. Goodwin, M.D., recent state medical association president, welcomed them into the association's 50 Year Club and awarded each an official lapel pin.

Mrs. T. A. Ragan, President of the auxiliary group, was in charge of general arrangements for the event which took place at the Officer's Club of the Norman naval base. Outstanding entertainment and buffet dinner were arranged by the Program Committee which was comprised of Mrs. W. H. Atkins, Chairman, Mrs. Carl T. Steen and Mrs. S. C. Bostic. Preceding the dinner and program, the Ragans and the Nielsens sponsored a social hour, also held at the club.

The Norman event typified the many Doctor's Day celebrations held throughout the state by County medical society auxiliaries.

Auxiliary News

Sooner Physician's Wife

The offical publication of the state auxiliary, the *Sooner Physician's Wife*, is issued quarterly to each dues paying member. Mrs. Samuel T. Moore, editor, Mrs. J. Powers Wolff, co-editor, and Mrs. Virgil Ray Forester, secretary-treasurer, all of Oklahoma City, work with the county press and publicity chairman in every county auxiliary in reporting news, projects and activities of the medical auxiliary.

Elizabeth Moore, editor in chief, is a journalism student and a writer. Mabel Wolff, a past president, has helped immeasurably with her knowledge of auxiliary matters. *Sooner Physician's Wife* is published by the Oklahoma City University Press.

Last year a colorful back cover was added which is attractive and distinctive. A display of bulletins and newsletters from other states was made at the Fall Conference at the State Medical Headquarters building. *Sooner Physician's Wife* compared most favorably with other state bulletins. We are proud of the quality and high standard of the state auxiliary publication.

More Members-at-Large

Members of an active auxiliary group may forget there are communities in Oklahoma with only a few doctors in a county, so there is no organized medical auxiliary to the county medical society. Sometimes two or three counties meet together. The wives of these doctors may be members-at-large of the state and national auxiliary, if the husband is a member in good standing of the county medical society and the Oklahoma State Medical Association.

Where there are five or more eligible auxiliary members who can meet at least four times a year, it is preferable that a county auxiliary be formed. The woman's auxiliary is a strong influence in community health programs or any such project that might be undertaken by the county medical society.

Members-at-large represent the auxiliary in their community. They can subscribe to the *National Bulletin, Today's Health* magazine, and read each issue of the *Sooner Physician's Wife* for information on current medical matters.

The Membership Committee, Mrs. Pat Fite, Sr., Muskogee, and Mrs. Tom C. Sparks, Ardmore, and the councilors in every district, have tripled the number of members-at-large this year.

Legislation

The auxiliary member is a voter, and often has valuable influence in the women's clubs, PTA, and other groups. In the matter of legislation, as with all other medical auxiliary programs, we look to the medical society for guidance. Last year the Jenkins-Keogh bill to encourage establishment of pension plans by the self-employed passed the House by an overwhelming vote, only to be stopped in the Senate. It has passed the House again this session and is about to be tested in the Senate.

The Forand bill, authorizing hospitalization and surgical benefits to all Social Security beneficiaries, is awaiting congressional consideration. Meanwhile, there is much community service to be done on the AMA program on Health Care of the Aged, our answer to the Forand bill.

Auxiliary members must keep informed and have close contact with the county medical society's legislation program in order to act intelligently when the need arises. The cooperation of auxiliary members who have complied with assistance on legislation requests, and those who have sent cards, telegrams and made personal contacts has been acknowledged and is deeply appreciated. Let us not relax our vigilance and continue to keep ourselves informed.

Today's Health the Magazine For the American Family

There are many projects undertaken by the Woman's Auxiliary that call for equal effort and support from the county medical societies. When the men have decided on a plan and outlined the course of action, the auxiliary is ready and eager to carry the project to completion. Their success in promoting the *Today's Health* magazine is a good example.

This official publication of the American Medical Association is written in the layman's language for the American family. It answers the familiar complaint that the busy doctor does not have time to explain medications, symptoms and new ideas in the mysterious world of medicine. This excellent magazine does it so well.

The physician's wife is asked many questions which apparently she is expected to know because she is married to this man of medicine. If she did know the answers, it is preferable that she not get involved in attempts to answer questions that lead her into deep water. The *Today's Health* magazine is the solution. Have a copy for reception room reading. Give subscriptions generously to neighbors, relatives, and those friends and acquaintances who expect information from the busy doctor; often taking more time and energy than he has to spare. Give subscriptions to teachers, preachers and community leaders who are called upon for leadership in health programs; they may need the authentic information provided through this AMA monthly publication for the general public—*Today's Health*—the magazine for the American family.

provides therapeutic levels . . . for 24 hours . . .
with low incidence of sensitivity reactions . . .
WHENEVER SULFAS ARE INDICATED
KYNEX
Sulfamethoxypyridazine Lederle
0.5 Gm. TABLETS/NEW ACETYL PEDIATRIC SUSPENSION
LEDERLE LABORATORIES, a Division of
AMERICAN CYANAMID COMPANY, Pearl River, New York

Have You Heard?

VAN HOWARD, M.D., a graduate of the University of Oklahoma School of Medicine in 1955, will open offices in the Hobart Clinic on July 1. Doctor Howard recently completed a three-year residency in surgery at St. Anthony Hospital in Oklahoma City.

WALLACE N. DAVIDSON, JR., M.D., Cushing, was recently certified by the American Board of Dermatology and is now serving three years at Wright Patterson Air Force Base Hospital, Dayton, Ohio, as head of the Department of Dermatology.

DOCTORS W. T. MCCOLLUM, ALLEN GREER and ROBERT REDMOND appeared before the Comanche County Medical Society's March meeting where they discussed cardiac catheterizations, angiograms, and cineradiography that is being performed at Mercy Hospital, Oklahoma City.

D. L. DYCUS, M.D., and K. H. BAGWELL, M.D., have recently opened the Moore Medical Clinic in Moore, Oklahoma. Both Doctors are graduates of the University of Oklahoma School of Medicine.

Deaths

A. S. Melton, M.D.
1885-1959

A. S. Melton, M.D., Okemah physician, died March 1, 1959.

Born in Marshall, Arkansas, Doctor Melton graduated from the University of Arkansas School of Medicine in 1912. After practicing in Rocky, Oklahoma for a short while, he moved to Okemah where he practiced for nearly thirty years.

Doctor Melton was serving his second term as President of the Okfuskee County Medical Society at the time of his death.

Albert E. Hennings, M.D.
1878-1959

Albert E. Hennings, M.D., died in Tuttle on February 28.

Born in 1878, Doctor Hennings graduated from St. Louis College of Physicians and Surgeons in 1907. He served as a member of the Oklahoma House of Representatives from 1947 to 1949.

In 1954, the Oklahoma State Medical Association honored Doctor Hennings for his service to the profession by presenting him with a Life Membership.

Alvin Ray Wiley, M.D.
1890-1959

Alvin Ray Wiley, 68-year-old Tulsa physician died March 13, 1959.

A native of Kansas City, Doctor Wiley came to Tulsa in 1903. He graduated from the University of Oklahoma School of Medicine in 1913.

Doctor Wiley concentrated his medical practice in the field of surgery. He was a Fellow in both the American College of Surgeons and the International College of Surgeons.

Active in both civic and professional work, Doctor Wiley was President of the Tulsa County Medical Society in 1939 and served for more than a decade on the Tulsa City Board of Health.

Harl F. Vandever, M.D.
1884-1959

Harl F. Vandever, 74-year-old Enid physician, died March 7, 1959.

A native of Minnesota, Doctor Vandever came to Oklahoma City in 1900. In 1907, he graduated from the University Medical College of Kansas City. He began his practice in Portales, New Mexico, moving to Lahoma, Oklahoma in 1910 and to Enid in 1912.

In 1957, Doctor Vandever was honored for his years of service to the profession when he was presented a Fifty Year pin by the Oklahoma State Medical Association.

Daniel William O'Leary, M.D.
1873-1959

Daniel William O'Leary, retired Norman physician, died March 24 in Norman. He was the father of Charles M. O'Leary, Oklahome City physician.

Born in LaFayette, Indiana, Doctor O'Leary graduated from the University of the South, Sewanee, Tennessee in 1904. He moved to Norman in 1941.

In 1950, Doctor O'Leary was honored for his years of service to the profession when he was presented a Life Membership in the Oklahoma State Medical Association.

Alvin W. Paulson, M.D.
1907-1959

Alvin W. Paulson, 51-year-old Oklahoma City physician, died on March 8, 1959. After graduating from Washington University School of Medicine in St. Louis in 1932, Doctor Paulson came to Oklahoma City where he practiced until 1934 when he moved to Clinton.

After six years in the military service, he practiced one year in Rapid City, South Dakota before joining the regional office of the Veterans Administration Hospital in Oklahoma City, a position he held at the time of his death.

25 YEARS AGO

Articles published in *The Journal* of the Oklahoma State Medical Association April, 1934.

RELIEF OF PROSTATIC HYPERTROPHY AND BLADDER NECK RESECTION BY THE TRANSURETHRAL METHOD

W. J. Wallace, M.D., Oklahoma City

Prostatic resection is the removal, by instruments passed through the urethra, of the obstructing portion of the prostate gland. This is carried out either by the improved cautery punch method, or by electrically controlled loops, which remove obstructing tissue under direct vision, and without resorting to the open operation.

Until within the last few years, it was considered that prostatic hypertrophy could only be relieved by the open operation, such as the suprapubic or perineal prostatectomy. Also until a fairly recent date the removal of the prostate was considered one of the most difficult and dangerous operations in the field of surgery.

Dr. Hugh Young, back in 1909, developed what is known as his punch instrument, which, so it is claimed, was fairly successful in certain types of obstruction, but not generally used on account of the likelihood of hemorrhage and infection.

Dr. John Caulk, in 1920, developed a cautery punch for cautery resection of prostatic obstruction. He believes that a large portion of the obstructions are inflammatory hyperplasias, and not neoplasms. Therefore, it is not necessary to remove the gland completely, but remove the obstructing portion, followed by a certain amount of shrinkage.

Stern, in 1926, introduced his ingenious instrument which he called the "resectoscope," but for some cause he did not continue his research work to a successful or practical conclusion. Shortly thereafter, though, Dr. T. M. Davis of Greenville, South Carolina, became interested and began using this instrument, but added numerous improvements, such as: A larger fenestra, cutting loop, improvement in the vision and lighting systems. He also added a coagulation current for the control of hemorrhage. So, to Dr. Davis, credit must be given for the advancement and information obtained in the transurethral method of treating the prostate and neck obstructions.

Credit is due, also, Dr. J. F. McCarthy for devising his ingenious visualizing instruments. At this time his instrument called the "resectotome," is fairly universally used.

There is no subject before the medical world today causing as much comment as the discussion of the relative merit of instrumental prostatectomy and other forms of vesicle neck obstruction. At this time there has been a sufficiently large number of cases reported and observed over a period of time, to permit one to make an estimate as to the relative merits of this method, as compared to the open operation. So, with the light of this information before me, I feel that at least 95 per cent of prostatic obstructions can be removed by the transurethral or instrumental method.

The question might be raised, "Will prostatectomy become obsolete, since the advent of the transurethral method?" I say "No," as there is no method that is one hundred per cent perfect. Then, too there might be complications that would end in more difficulty, which might require either suprapubic or the perineal operative measures, but the percentage of use of the older method will be small, I think not over five per cent.

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PHYSICIAN PLACEMENT

General Practice

Albert Stanley Bailey, Jr., M.D., P.O. Box 1381, Westhampton Beach, L. I., New York, age 28, married, graduated from University of Oklahoma, 1955, presently in military service, will be available May, 1959.

Johnny Bill Delashaw, 1905 1st Avenue, N., Texas City, Texas, age 25, married, graduated from University of Texas Medical Branch, 1959, will be available upon completion of internship, July, 1960.

John W. Kennard, M.D., 20 Olson Lane, Fort Rucker, Alabama, age 26, married, graduated from Bowman Gray School of Medicine, 1956, presently in military service, will be available September, 1959.

James W. McDoniel, M.D., 13-B Thompson Street, Langley Air Force Base, Virginia, age 27, married, graduated from Oklahoma University School of Medicine, 1956, will be available July 1, 1959.

Robert Emmett Myers, M.D., 872 Ravine Drive, Cleveland 12, Ohio, age 28, married, graduated from University of Arkansas, 1955. Would like to do general practice with emphasis on pediatrics, veteran, will be available September, 1959.

Edwin Ruben Reinschmiedt, Lt., MC, USNR, BOQ, Alameda Naval Air Station, California, age 30, married, graduated from University of Oklahoma, 1956, presently in military service, will be available June 15, 1959.

Wyatt Bibb Pouncey, M.D., 118 Louise Lane, San Mateo, California, age 34, married, graduated from University of Alabama, 1950, veteran, available immediately.

Robert Glenn White, Jr., M.D., 431 Saratoga, San Antonio, Texas, age 26, married, graduated from University of Oklahoma, 1956, presently in military service, will be available August 2, 1959.

Gerald C. Zumwalt, M.D., 1701 Avenue P, Del Rio, Texas, age 27, married, graduated from University of Oklahoma, 1956, veteran, will be available July, 1959.

Internal Medicine

William S. Harrison, M.D., 2623 Pittsfield Blvd., Ann Arbor, Michigan, age 31, married, graduated from University of Oklahoma School of Medicine, 1953, veteran, will be available September 1, 1959.

Locum Tenens

Don Allen Mills, M.D., 3911 Burns Place, S.E., Washington, D.C., age 34, married, veteran, graduated from Georgetown University School of Medicine, 1958, wants to do general practice for two years prior to specialized training. Will be available July 1, 1959.

Neurology

Kenneth C. Duncan, M.D., St. Luke's Hospital, Chicago, Illinois, age 30, married, graduated from the University of Oklahoma, 1955, veteran, will be available July, 1959.

Obstetrics and Gynecology

Milton Gardner Mutch, Jr., M.D., 423 Mills Avenue, Fargo, North Dakota, age 31, married, graduated from University of Minnesota, 1955, will be Board eligible upon completion of fellowship, veteran, will be available July 1, 1959.

Pediatrics

Prentiss Edwards Findlay, M.D., 1500 Wakefield Place, New Orleans 22, Louisiana, age 29, married, graduated from Emory University, Atlanta, 1954, noneligible for military service, will be available July 15, 1959.

Surgery

(Name on Request) 32 years old, married, graduated from Tulane, 1952, veteran, board eligible in surgery.

Valerio J. Federici, M.D., 2401 West Toronto Street, Philadelphia, Pennsylvania, age 36, married, graduated from Jefferson Medical College, 1948, veteran, is now available.

Owen Foster Kline, Jr., M.D., 4712 Warrington Drive, Flint, Michigan, married, graduated from University of Colorado, 1954, not eligible for military service at the present time, will be available July 1, 1959.

General Surgery

Clyde William Draughon, M.D., McGuire Hospital, Box 27, Richmond, Virginia, age 35, married, graduated from University of Oklahoma School of Medicine, 1954, veteran, will be available July 1, 1959.

Tuberculosis

Helen C. Sharp, M.D., 620½ N. Broadway, Pittsburgh, Kansas, single, graduated from University of Kansas, 1928, prefers to do industrial or student health work and is presently available.

MISCELLANEOUS ADVERTISEMENTS

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1600 SQUARE FOOT physician's office and home for sale, located in Oklahoma community of 10,000. Office may be purchased separately, or both may be bought for about one year's gross income. Excellent practice opportunity at moderate cost. Write Box A, The Journal, Oklahoma State Medical Association, P. O. Box 9696, Oklahoma City, Oklahoma.

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